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IN OCTOBER, 1920, the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY was presented to the medical profession for its approval in the belief that the importance of obstetrics and gynecology as integral parts of medical art and science merited and would warrant the publication of a monthly periodical dedicated to this specialty.

From its beginning the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY has been conducted by medical men in the interests of the profession, with the general conduct of the enterprise vested in an advisory editorial board, the membership of which should serve as a guarantee that these interests have been adequately protected and assured. A liberal editorial policy has been maintained toward the specialist as well as the general practitioner of medicine, and we believe that this catholicity has contributed greatly to the value of the publication.

The success of the JOURNAL may be measured by the demands of contributors for space in its columns. Twice since its founding have the number of pages per volume been increased until it was felt that the practical limits of expansion had been reached. It was therefore found necessary to restrict the privilege of publication to American authors, and numerous applications from foreign sources have been regretfully declined.

The editors and publishers are happy to record the successful career of the JOURNAL, both in circulation and popularity. The JOURNAL now represents in an official capacity the national and most of the local gynecologic and obstetric societies of the United States and publishes their papers and proceedings. In addition the various departments, each with its responsible editor, have grown in importance. The Abstract Department in particular has expanded until it includes 27 members familiar with all the living languages, so that it is possible in a limited space to acquaint our readers with the progress of the world in obstetrics and gynecology.

The JOURNAL has reached now the tenth milestone in its progress. The task of building has been a difficult one and for the editors almost solely a labor of love. But we feel that it has been a worth-while effort and we are proud of the success thus far attained. We are grateful to the many friends who, by their help and counsel, have stimulated us in this work, and to the many contributors and subscribers who have made possible the material success of the venture. Deeply interested as we have been in the growth and development of the JOURNAL, it is but natural for us to hope that many milestones may yet be needed to record its further progress.

GEO. W. KOSMAK, M.D.
HUGO EHRENFEST, M.D.

Original Communications*

POSTSALPINGECTOMY ENDOMETRIOSIS (ENDOSALPINGIOSIS)

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THE healing of operative wounds has been of great scientific and clinical interest to the medical profession. For these reasons a vast amount of work has been done in the study of this process both in lower animals and in human beings. The appearance of appendicectomy scars suggests, and a review of the literature on intestinal repair demonstrates the remarkable manner in which the healing of operative wounds of the intestine occurs with the preservation of the normal relation between the mucosa and the wall of the viscus. From these studies we realize that the healing of operative wounds of hollow viscera are governed by a most important and fundamental law. This law might be stated as follows: the growth of the epithelium of a hollow viscus, which has been initiated by operative injury, is confined to the repair of the lining of the viscus; it does not actually invade the wall of the organ; it ceases to grow when the wound is healed and when transplanted in immediate or remote operative wounds it does not live. Fortunately for both patient and surgeon this law is generally obeyed. While violations do occur in the healing of intestinal wounds they are infrequent, often transitory and usually of minor significance. There is one striking exception to this rule, and that is the behavior of tubal epithelium in the repair of salpingectomy wounds. This is shown in our study of tubal stumps following salpingectomy and tubal sterilization, as will be discussed later.

There is an old saying, homely but fitting and true, that "good fences speak for good neighbors." The fences, some easily seen and others invisible, which are placed in and about the tissues of the human body, are good fences. They both protect and restrain, and thereby preserve tissue balance which speaks for harmony and the welfare of

*All of the papers published in this issue were read at the Fifty-fifth Annual Meeting of the American Gynecological Society held at Hot Springs, Va., May 19-21, 1930. The remaining papers and the discussions will appear in the November issue of this Journal.

the individual. We have learned that as a result of operative injury fences are torn down and tissue balance is disturbed. This is followed by the process of repair. Should the organ or structure injured be lined or covered by epithelium, epithelial as well as connective tissue cells grow and take part in the repair of the injury. As a result fences are repaired, tissue balance is fully restored and the normal relation between epithelium and connective tissue is usually preserved.

The examination of the head of the cecum, after a previous operation in which the appendix has been removed, demonstrates that the site of the appendicectomy usually differs in no way from the rest of the cecum save for the possible presence of a scar on its peritoneal surface. This is irrespective of the technic of the operation, whether it be simple ligation of the stump, ligation with invagination or excision with closure of the opening in the cecum. There is no gross evidence of an invasion of the walls of the viscus by its mucosa such as can readily be detected in a large percentage of salpingectomy stumps.

Mall[1] made a very important contribution to our knowledge of the repair of operative wounds of the intestine, in his study of the healing of circular suture (end-to-end anastomosis) of dogs' intestine. He divided the repair of these wounds into four stages: (1) the immediate union of the serous surfaces by fibrin; (2) the destruction of redundant tissue in the flaps; (3) the regeneration of the mucosa, and (4) the straightening of the intestine at the site of the repair. He found that at the end of two months all the intestinal coats were fully regenerated. The line of suture could hardly be detected microscopically while macroscopically it was marked by a thickening of the intestinal wall. In some of the specimens the mucosal glands had apparently invaded the wall of the intestine, at times forming "adenomatous cysts." Mall believed that this arose from the downward growth of the epithelium into rents in the intestinal wall caused by sutures penetrating the mucosa and tearing the submucosa. He states: "It is possible that these cells, when once fully liberated, could do considerable mischief."

Sabin[2] has reviewed Mall's work and from her own studies of the healing of intestinal anastomoses she explained the lack of clinical significance of the downward growth of mucosal glands into breaks in the intestinal wall. She believes that the subsequent growth (repair) of the muscularis mucosae about these newly formed glands restores them to their normal position in the mucosa.

Flint[3] described the results of the healing of gastroenterostomies based on a series of experimental work in animals. He found that there was always a regeneration of the mucosa and submucosa but that the repair of the muscularis mucosae and muscle layers was generally incomplete. The epithelial cells appeared to regenerate in an orderly manner and did not actually invade neighboring structures. When the muscularis mucosae was torn or failed to regenerate glands of the mucosa might grow down into the submucosa.

McWhorter, Stout and Lieb[4] reported the process of repair in sutured wounds of the small intestine. They examined more than thirty-two specimens, and compared their observations with those reported in the literature. They stated that after two months the mucosa was completely regenerated and could not be distinguished from the surrounding undamaged mucosa. Complete anatomic regeneration of the muscularis did not occur. A realignment of the infolded muscular fibers took place but it was always interrupted by a thin line of scar tissue. The cysts

and tubules of intestinal mucosa in the walls of the intestines described by Mall were observed by these writers in four of their cases. They usually occurred about buried sutures and appeared to be of purely pathologic interest and not of any surgical importance.

Fraser and Dott,[5] in describing the results of their experimental intestinal anastomoses in dogs, speak of the "extraordinary powers of adaptation and reconstruction which the tissues of the bowel possess. The mucous membrane showed perfect regeneration." In cases of ileocolostomy the mucous membrane of the small intestine, within a few millimeters of the junction, underwent a metamorphosis to a colonic type. Even in this operation it was impossible to identify the mucous membrane junction after about eighty days.

Lee[6] in the discussion of his experimental end-to-end anastomosis of the colon in dogs states that in all of the anastomoses, which were thirty days old or more, the mucosa had healed completely. He found that "the mucosal glands at the site of anastomosis were much larger than the ordinary ones, with individual cells longer, and with much greater evidences of cell proliferation. Moreover, these large young glands showed marked cell division in certain regions in which the cells were embryonic in character and where they invaded the connective tissue stroma in a lawless cancer-like manner. Finally, small islands of very young epithelial cells, which were usually cross-sections of the base of incomplete crypts and which probably arose from a nucleus of a few cells taken from the base of normal glands at the time of operation were also observed at the site of anastomosis." Mall[7] states that "it is quite characteristic of epithelial cells to grow somewhat profusely in the neighborhood of wounds. In the alimentary canal and skin these newly formed cells often grow into depth, probably only to be destroyed when the equilibrium is again brought about."

The inspection of appendicectomy scars in human beings and the histologic study of the results of intestinal repairs and anastomoses in the lower animals demonstrates the remarkable manner in which healing results with the preservation of the normal relation between the mucosa of the viscus and its wall. This occurs irrespective of the type of operation or the part of the intestinal tract involved. When intestinal mucosa was found extending into the wall of the intestine of the lower animals it was shown that it was usually due to the filling or lining of breaks in the wall of the intestine, arising from faulty technic and rarely from the actual invasion of the intestine by the mucosa. When epithelium is transplanted in the immediate operative wound and lives, its life may be temporary, at least it apparently is of no clinical significance.

The repair of salpingectomy wounds is one exception to the law of normal healing of hollow viscera as has been already stated. In a very large percentage of these cases the growth of tubal epithelium, initiated by operative injury, not only actually invades the tubal stump and sometimes any structure adherent to it but it also may continue to grow after healing has occurred. Seedlings are also sometimes found in situations where bits of tubal mucosa might have been misplaced (transplanted) at the original operation.

The results of a histologic study of tubal stumps following salpingectomy or tubal sterilization in thirty-six patients were described by

the writer[8] two years ago. Misplaced müllerian mucosa occurring either as "sprouts" from the mucosa of the stump, as "seedlings" or both, were found in thirty of the thirty-six cases. During the last two years we have collected and studied stumps from sixty-four additional patients and have adopted methods in their study which have been of great help to us. It is the purpose of the present paper to review these hundred cases, to emphasize again the frequency of postsalpingectomy endometriosis (endosalpingiosis) and its scientific and clinical importance with the hope that others may be prompted to study the conditions resulting from the healing of salpingectomy wounds. In this way we should learn more about the origin of ectopic müllerian

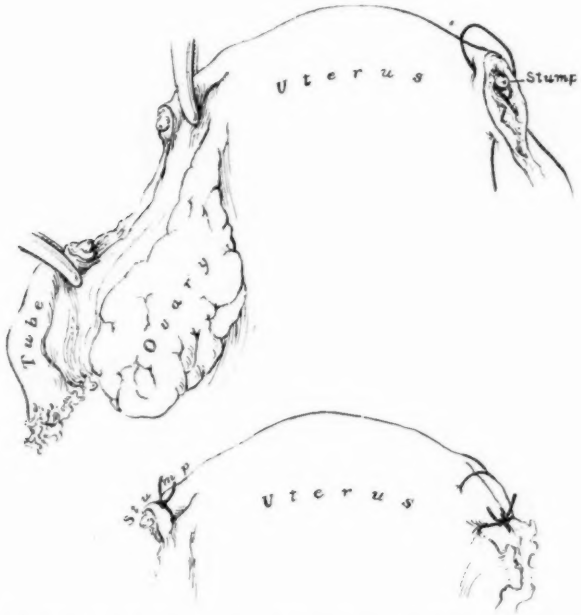

Fig. 1.—The two usual types of salpingectomy (×2/3). Many operators sever the tube distal to the uterus, often between two clamps, and ligate the stump without burying it. Others (as is our practice) remove the tube close to the uterus or excise a wedge-shaped piece of the uterine cornu and bury the stump in the cornu. In the healing of salpingectomy wounds of the first group we must account for the "nubbin" of the tube distal to the ligature and also for the behavior of the tube traumatized by the ligature and possibly crushed by a clamp. In the second group we must study the reaction of the traumatized and buried interstitial portion of the tube in the uterine cornu.

mucosa and be able to employ better judgment and technic in operations requiring salpingectomy or tubal sterilization.

In the repair of salpingectomy wounds, the mucosa of the tube, its wall and the tissue in which the stump is buried (if the latter technic is employed) all take part in this process. We must determine the fate of the tubal mucosa which is always traumatized and sometimes misplaced (transplanted) in these operations. To do this intelligently we should know the type and technic of the salpingectomy. This is

often difficult to obtain. The conditions found at the second operation will usually indicate whether or not the tube was severed distal to the uterus but further details may be lacking. In this type of salpingectomy the stump is ligated and often clamped prior to the application of the ligature. We must account for the "nubbin" of the tube distal to the ligature and the fate of the tubal mucosa in this "nubbin." One must also account for the behavior of the tubal epithelium traumatized by the ligature and possibly crushed by a clamp. Should the stump be buried in the uterine cornu, the interstitial portion of the tube is not only traumatized by severing it but it may also

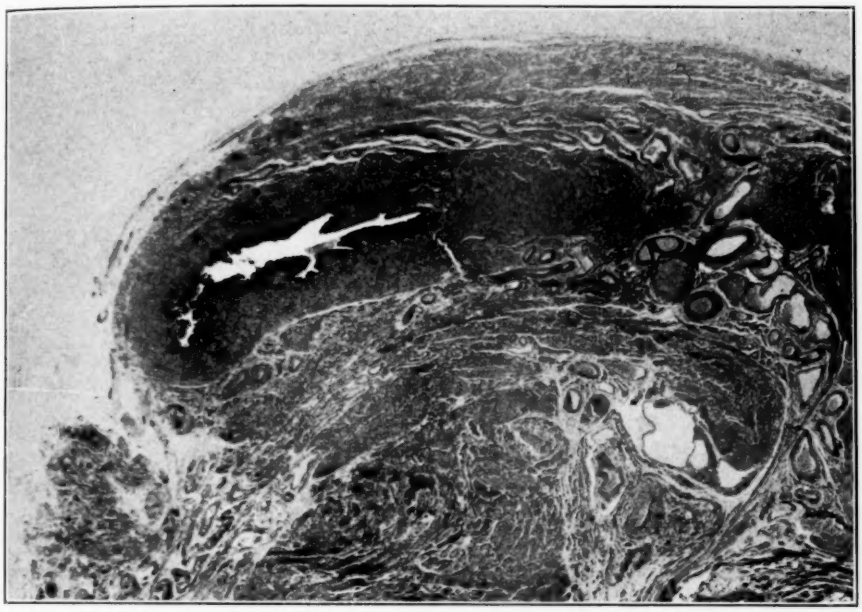

Fig. 2.—Photomicrograph (×10) of a longitudinal section of a tubal stump showing normal healing. The "nubbin" of the tube, distal to the ligature (see Fig. 1) apparently has sloughed away and has been absorbed. The end of the stump (to the left) is closed by the tissues of its wall growing over the lumen without the presence of ectopic tubal mucosa either in the stump or in other structures of the salpingectomy wound. Normal healing is the exception, less than 24 per cent in 147 stumps. Both tubes and one ovary had been removed for bilateral salpingitis, nine years before the last operation. Indications for the latter were pain (pelvic adhesions) and profuse menstruation.

be injured by sutures compressing it and passing through it (Fig. 1). Even in attempted excision of the interstitial portion of the tube, the latter may not be entirely removed. In all of these operations bits of tubal mucosa may sometimes be misplaced (transplanted) in immediate or remote operative wounds. What happens to the traumatized and misplaced tubal epithelium? Some of it undoubtedly is destroyed by the operation but that which is not, as well as the near-by untraumatized epithelium, must take part in the process of repair.

What constitutes normal healing of a salpingectomy wound? Obviously a tubal stump, the end of which is closed by the tissues of its wall growing over its lumen and without the presence of ectopic tubal mucosa either in the stump or in other structures of the salpingectomy wound (Fig. 2).

In studying the results of the repair of salpingectomy wounds we must bear in mind that ectopic müllerian mucosa, from various sources,

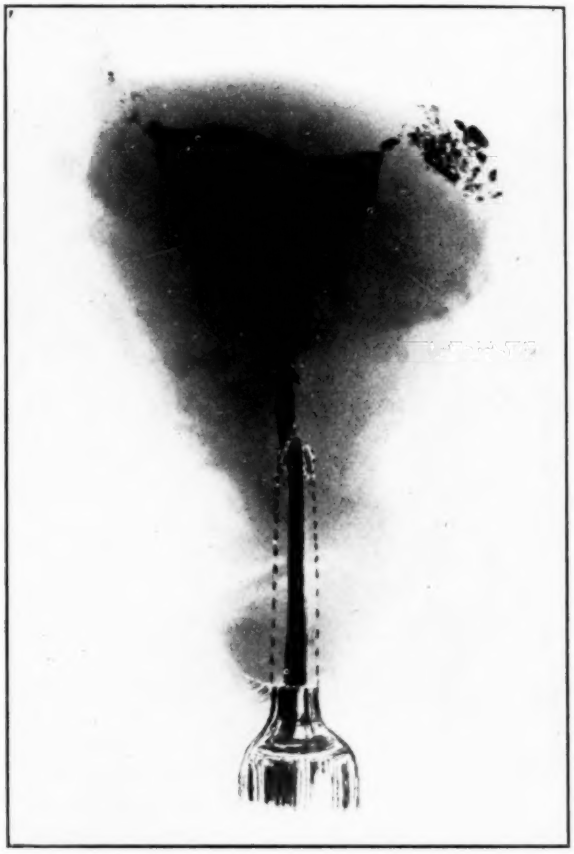

Fig. 3.—Roentgenogram (×1) of a uterus with endosalpingiosis of both uterine cornua (of nonoperative origin). The uterine cavity is filled with gelatin containing bismuth sub-carbonate which has escaped into the lumina of the tubules of the endosalpingiosis of the uterine cornua (more extensive on one side). The syringe inserted in the cervical canal indicates this method of studying endosalpingiosis both of intact tubes and also of tubal stumps.

occasionally is present in the uterine cornu and isthmus of the tube of patients who had not had a previous operation, and that this might have been present at the time of the salpingectomy. This was considered by the writer in the first series of cases reported by him.

In the discussion of this paper Novak[9] stated that he could duplicate practically all of the conditions presented by me from sections of the

interstitial portions of tubes which had not been removed but which were still attached to the uterus and emphasized the importance of studies of the interstitial portions of normal and inflamed tubes before drawing any conclusions as to the changes which I had described following salpingectomy. Everett[10] confirmed Novak's observations. I had been studying misplaced müllerian mucosa in the uterine cornu and in the tubal wall for several years, and had been impressed with its relative infrequency as compared with that found in and about salpingectomy stumps. However, this condition had not been studied with the same care as salpingectomy stumps.

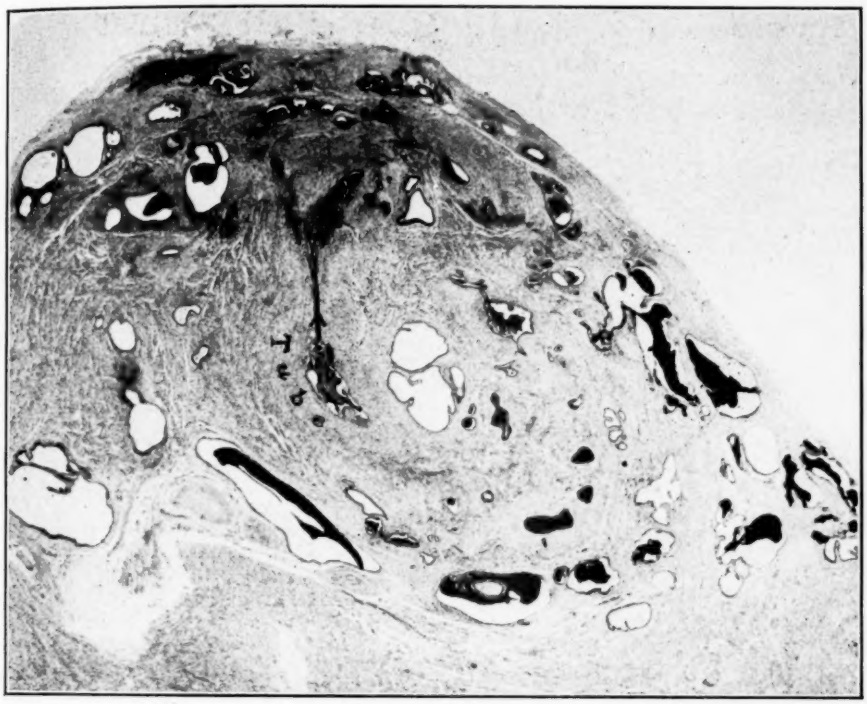

Fig. 4.—Photomicrograph (×10) of a section of the uterine cornu, with the more extensive endosalpingiosis shown in Fig. 3. The interstitial portion of the tube appears in cross-section with a tubule arising from it and branches of the latter spreading out into the tissues of the uterine cornu (see arrows). Note that the tubules have extended almost to the peritoneal surface. The misplaced müllerian mucosa is everywhere of tubal type. In my experience endosalpingiosis of nonoperative origin very rarely presents the typical histologic structure of the uterine mucosa (compare with Figs. 13 and 14). Some of the tubules are empty and in others the injection mass is shrunken. Unfortunately, in handling the sections, the shrunken injection mass often drops out of the lumina of some of the tubules.

This last year, therefore, I made a careful study of the uterine cornu and the first part of the isthmus of the tube in 100 of 104 consecutive uteri from patients who had not had a previous operation. Four of the uteri were preserved as museum specimens and were not utilized.

Hoehne[11] in 1905 demonstrated, by the injection of gelatin containing Berlin blue, the connection between the lumen of the tube and the

branching intramural tubules present in nonoperative endosalpingiosis. The lumen of the tube was injected by a syringe inserted in its ampulla. I employed the same principal as Hoehne but with a different technic. The uterine cavity was injected through the cervix with gelatin containing a pigment (Fig. 3). Bismuth subcarbonate, graphite, lamp black and ultra-marine blue were used. They were all satisfactory except graphite. The latter gave good injections but dulled the microtome knife. After injecting the uterine cavity and forcing the mass into the lumen of the tubes, the syringe was withdrawn, cervix clamped, and the uterus placed in ice water until the gelatin had become solidified. The uterine cornu and the first part of the isthmus of the tube were excised, hardened in formalin and completely sectioned. Misplaced müllerian mucosa was found in thirteen

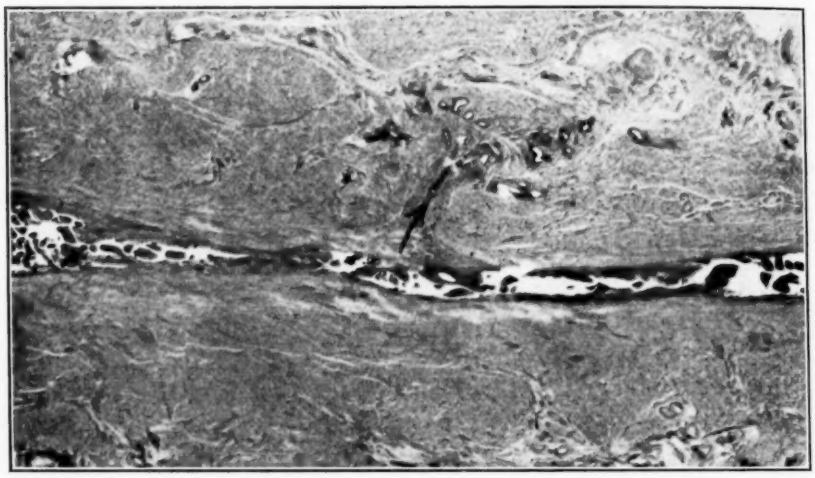

Fig. 5.—Photomicrograph (×10) of a longitudinal section of the interstitial portion of a tube showing a very early endosalpingiosis of nonoperative origin. The tube is patent as were those shown in Fig. 3. In order to fill the tubules of a nonoperative endosalpingiosis with the injection mass, it is often necessary to clamp or ligate the tube distal to the uterus. Otherwise the mass will all escape through the lumen of the tube if the latter is patent as it often is in this condition.

of the one hundred cases. Two were associated with a peritoneal endometriosis which had invaded the uterine cornu from its peritoneal surface: these were of endometrial type. In two instances the uterine cornu had been invaded by the mucosa of the uterine cavity, which also was of endometrial type. In eight cases the uterine cornu had been invaded by the mucosa of the interstitial portion of the tube. These were all of tubal type (Figs. 4, 5 and 6) as well as the one instance of endosalpingiosis of the isthmus of the tube. Of the thirteen cases only three were bilateral, thus making sixteen instances of misplaced müllerian mucosa in two hundred uterine cornua. Eighteen of the one hundred patients showed gross evidence of an existing or previous salpingitis, four of the nine instances of primary endosal-

pingiosis occurred in this group, thus emphasizing the importance of infection as a cause of this condition. The uterine cornua were studied from thirty-two additional uteri with gross evidence of tubal infection. In the fifty cases of this group a primary endosalpingiosis was found in fourteen. Five of these were bilateral, thus making nineteen instances of misplaced müllerian mucosa in one hundred uterine cornua associated with tubes presenting gross evidence of an existing or previous infection.

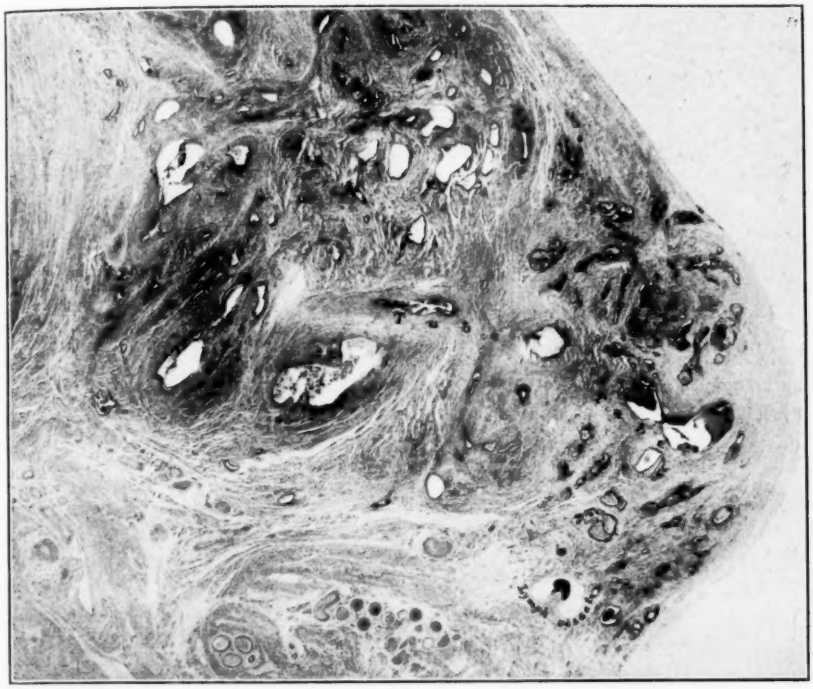

Fig. 6.—Photomicrograph (×6) of a section of a uterine cornu in a plane corresponding to a cross-section of the uterus; uterine cavity injected with gelatin containing lampblack. Both tubes and one ovary had been removed, a year before, for "salpingitis." The tube apparently had been severed close to the uterus, and possibly its stump was buried. The interstitial portion of the tube appears in longitudinal section. A similar endosalpingiosis was present in the opposite uterine cornu. Circumstantial evidence indicates that endosalpingiosis was present in both uterine cornua at the first operation. The distal portion of this might have been of operative origin. Note the lymph vessel with müllerian tissue apparently implanted on its wall (see F.g. 7). The indications for the second operation were pelvic pain and slight uterine bleeding. Many adhesions were found at that operation and evident metastases of cancer in the pelvic lymph nodes. On incising the uterus, after its removal, a small cancer of the cervical mucosa was found. Had the uterus been removed at the first operation the second would not have been necessary, and possibly the patient's life might have been spared.

A REVIEW OF THE RESULTS OF THE HEALING OF SALPINGECTOMY WOUNDS IN ONE HUNDRED PATIENTS (INCLUDING THE THIRTY-SIX PREVIOUSLY REPORTED)

I have been studying tubal stumps for about four years. Four specimens were from autopsies (courtesy of Dr. V. C. Jacobsen) and the

remaining, either uteri or the excised stumps, were obtained at operation by members of the gynecological staff of the Albany Hospital. As bilateral salpingectomy or tubal sterilization had been done in forty-seven of the patients, one hundred and forty-seven stumps, many with other structures adherent to them, were available for histologic study.

In all instances the stump including any structure adherent to the same was completely sectioned and studied. The blocks were embedded in celloidin and the sections stained in hematoxylin and eosin. The entire course of the lumen of the tube in the stump was followed and its relation to any misplaced müllerian mucosa was determined.

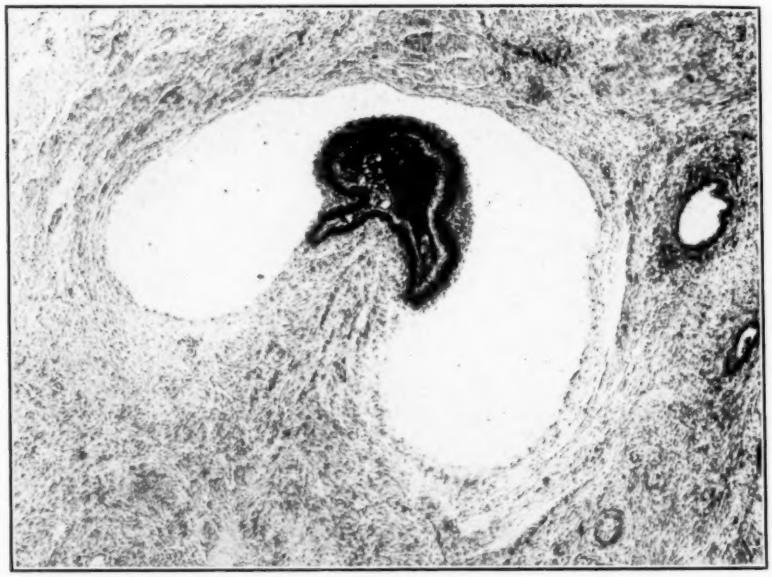

Fig. 7.—Photomicrograph (×60) of the lymph vessel shown in Fig. 6. The müllerian tissue, apparently of metastatic origin, is in reality a cross-section of a tubule, the lumen of which is filled with the injection mass. This mass had been introduced into the uterine cavity through the cervix. Serial sections of this portion of the block also demonstrated the origin of the tubule from the portion of the tube above it. The origin and course of injected tubules can be followed as readily as the course and branches of an injected blood vessel.

By carefully watching the surface of the block, as the sections were cut, one could see the tube follow its course, detect any misplaced müllerian mucosa, if present, and usually determine its relation to the mucosa of the tube. The effect was that of watching a slowly moving motion picture. The interesting sections were stacked in their sequence and stained and mounted. In places, where there was doubt as to the condition present, complete serial sections were saved and mounted. All other sections were saved until the specimen had been completely studied. In forty-three instances the uterine cavities were injected with gelatin containing a pigment as in the study of the one

hundred uteri with intact tubes. We found that this was of great assistance. The origin of any sprouts and their course was traced as readily as the course and branches of an injected blood vessel and with greater ease and accuracy than in the noninjected specimens. This feature of the work was entrusted to Miss Isabel Peck, who is well trained in histologic technic and in the diagnosis of müllerian tissue.

Normal healing, i.e., occlusion of the distal end of the tubal stump without the presence of ectopic müllerian mucosa occurred in only thirty-five of the one hundred and forty-seven stumps studied. Misplaced müllerian mucosa was found in one hundred and twelve of the one hundred and forty-seven stumps as compared with sixteen instances in two hundred controls from uteri with intact tubes and nineteen instances in one hundred controls from uteri with gross evidence of salpingitis. The distal end of the stump was proved to be patent in only three instances.

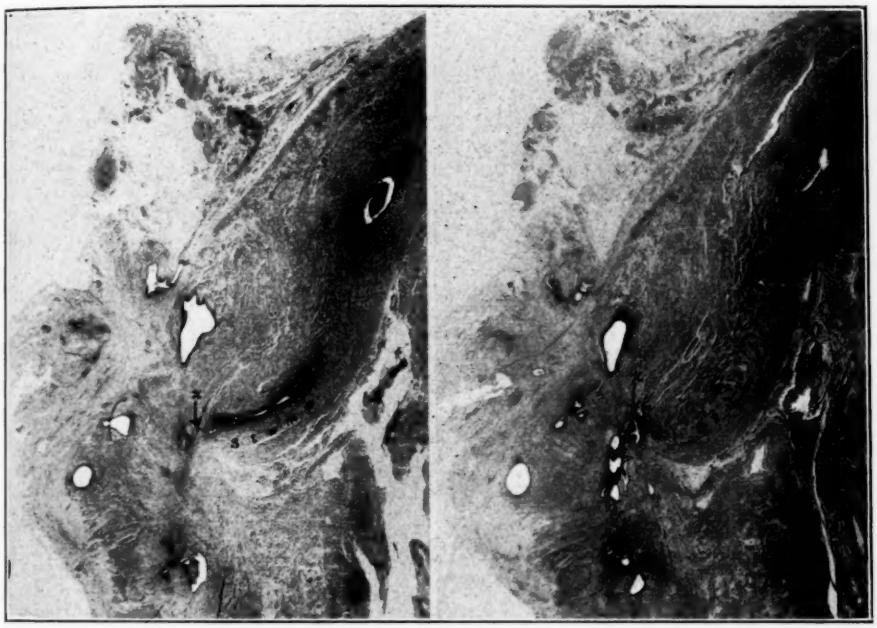

Fig. 8.—Two photomicrographs (×6) from a series of longitudinal sections of a tubal stump; uterine cavity not injected. At the first operation a year before, tubal sterilization had been done and the uterus fixed to the abdominal wall. Indications for the second operation were a sense of lack of support and severe menstrual pain. The uterus was retroflexed and pelvic floor relaxed. At operation, the appendix, uterus and left tube and ovary were removed and pelvic floor repaired. From conditions found at this last operation, evidently a piece of the tube had been excised at the first operation. Sprouts (terminal) have arisen from the outgrowth of tubal mucosa from the end of the stump. Had the uterine cavity been injected the origin of the misplaced müllerian mucosa about the stump could have been more accurately determined.

This ectopic mucosa in and about stumps falls into two groups: first, sprouts which arise from a direct outgrowth of the mucosa of the stump, and second, seedlings which are not continuous with the tubal mucosa. The sprouts are of two kinds, terminal, arising from the distal end of the stump, and lateral, growing out from the side of the stump.

The sprouts must have arisen either during the repair of the stump traumatized by the operation or independent of it. If independent, they might have been present at the time of the salpingectomy or developed after healing had occurred. Is it possible to determine, from the histologic study of the stump whether or not the endosalpingiosis,

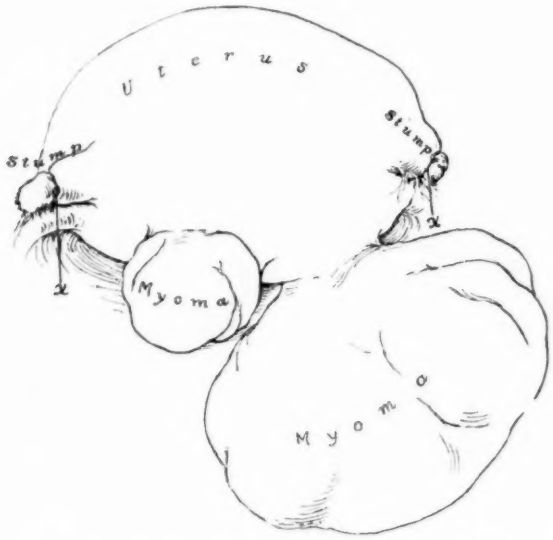

Fig. 9.—Fundus of the uterus with multiple myomata (×2/3). Both tubes had been removed eighteen years before for "salpingitis." At the last operation, by Dr. Lyle A. Sutton, the appendix, uterus and left ovary were removed. The uterine cavity was injected with gelatin containing lampblack. The tubes had obviously been severed distal to the uterus at the first operation and the stumps ligated at X and X. (See Figs. 10 and 11.)

present, was of operative origin? I believe that it is often possible. In only three of the cases in which a unilateral salpingectomy had been done at a previous operation, was an endosalpingiosis of the same type and in the same relative situation found in both uterine cornua. In these three cases, I believe that the process in the stumps was probably of nonoperative origin. When the tube is severed distal to the uterus and an endosalpingiosis is found arising from the interstitial portion of the tube it is probably of nonoperative origin. When the sprouts arise from the distal end of the stump (Fig. 8), or if lateral (Figs. 9, 10 and 11) arise in the portion of the stump which is constricted (apparent site of ligation), circumstantial evidence indicates

that these are of operative origin. In a few instances endosalpingiosis of apparently both operative and nonoperative origin were found.

In my experience endosalpingiosis of nonoperative origin is usually of tubal and not of endometrial type (Figs. 4, 5 and 6). The cross-sections of the sprouts may so closely resemble the portion of the tube from which they arise that it is often difficult to determine which is the lumen of the tube. I have seen only one instance in forty-five specimens recently studied in which the tubules arising from the tubal

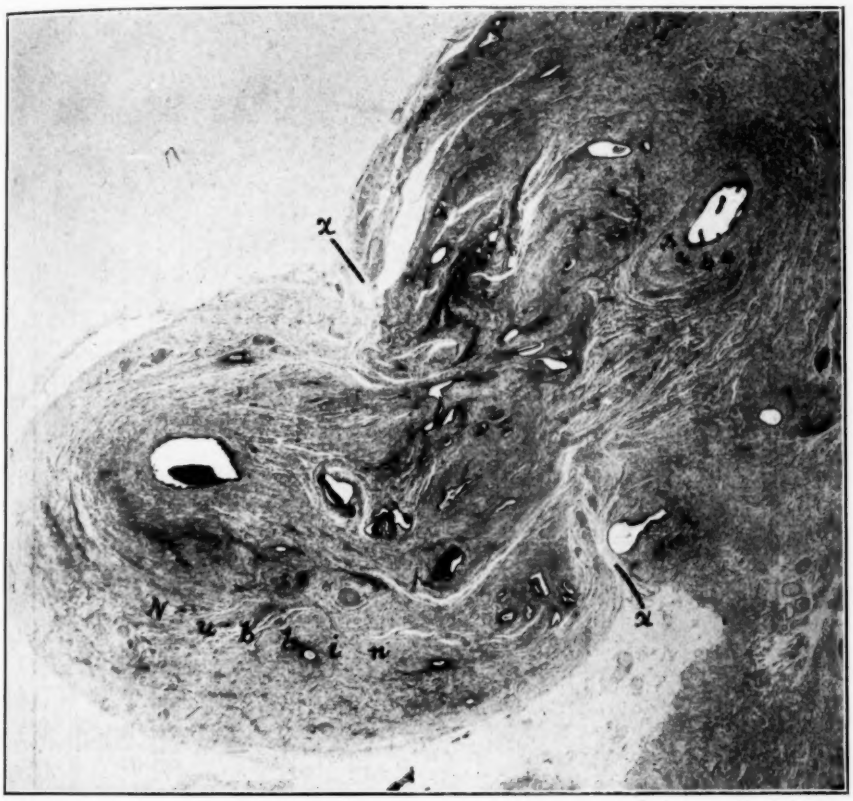

Fig. 10.—Photomicrograph (×10) of a longitudinal section of the right tubal stump shown in Fig. 9. Apparently the stump had been ligated at X, and the "nubbin" distal to the ligature did not slough off. Normal healing occurred at the distal end of the "nubbin" but in the attempted repair of the portion of the stump traumatized by the ligature an endosalpingiosis resulted. The injection mass can be seen in the lumina of some of the sprouts.

mucosa, presented the histologic structure of typical uterine mucosa. On the other hand, the sprouts of operative origin often take on the structure of typical uterine mucosa. This change was found in twenty stumps (Figs. 13 and 14).

The very large percentage of tubal stumps with endosalpingiosis (over 76 per cent in 147 stumps) as compared with the incidence of endosalpingiosis in intact tubes (8 per cent in 200 controls) leaves no

doubt as to the operative origin of this process in the majority of the stumps. In fourteen patients who had had tubal sterilization, endosalpingiosis was present in eleven and in all but one instance was present in both sides. When tubal sterilization is done the tubes are

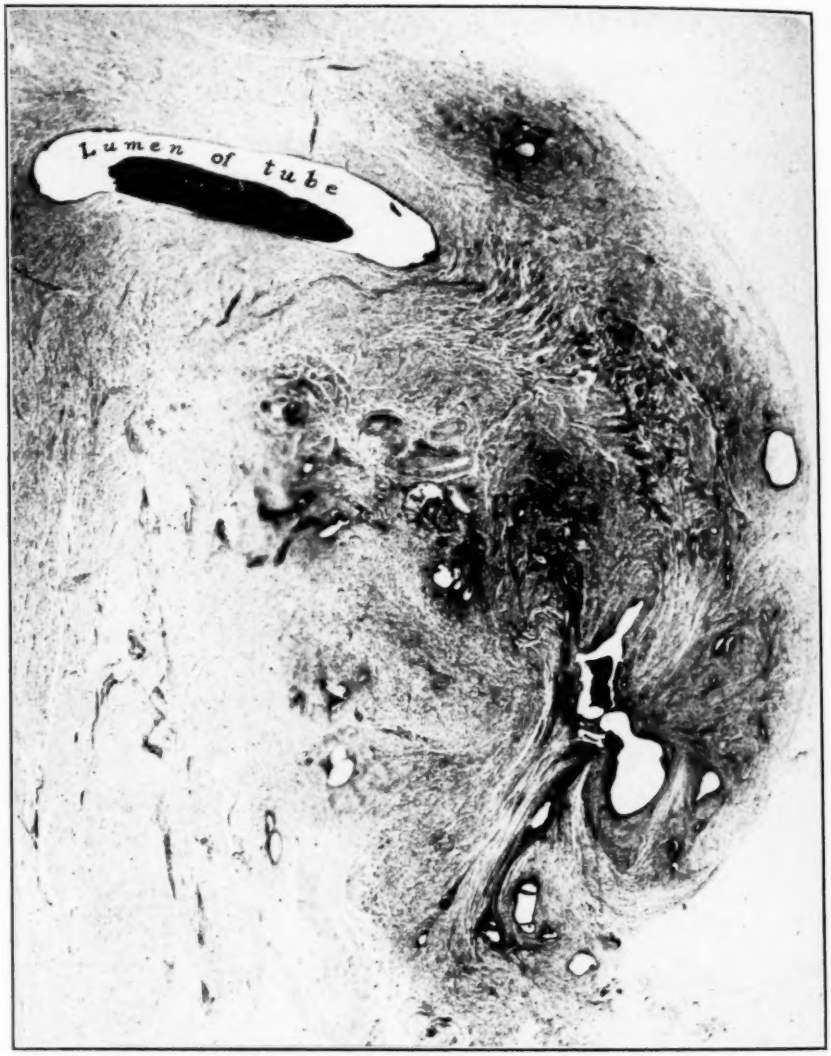

Fig. 11.—Photomicrograph (×10) of a longitudinal section of the left tubal stump in Fig. 9. An endosalpingiosis apparently has developed in the portion of the stump traumatized by the ligature.

usually normal and there is very little likelihood of an existing endosalpingiosis. In the patients with bilateral salpingectomy when endosalpingiosis was present in one stump it was also usually present in the other.

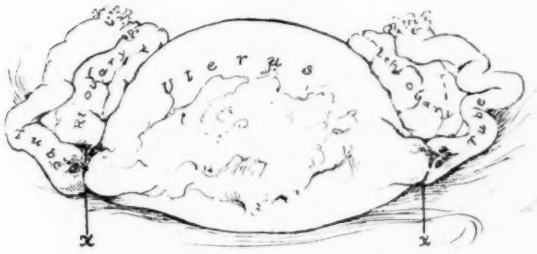

Fig. 12.—Fundus of the uterus with tubes and ovaries (×2/3); tubal sterilization by ligating the tubes close to the uterus with No. 2 chromic catgut, and ventrofixation had been done four years before the last operation. Indications for the last operation were pelvic pain and irregular uterine bleeding. Uterus and left tube and ovary were removed; uterine cavity injected with gelatin and lampblack. Constrictions evidently caused by the ligation of the tubes are indicated by X and X (see Fig. 13).

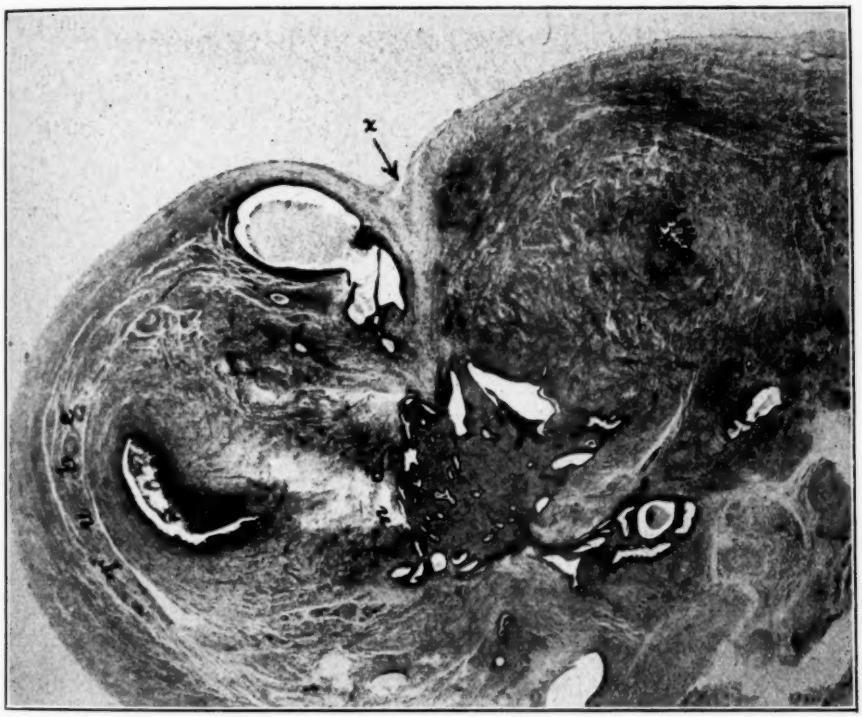

Fig. 13.—Photomicrograph (×10) of a longitudinal section of a portion of the right tube at the site of tubal sterilization (Fig. 12). The evident site of ligation is indicated by X. The "stump" is separated from the rest of the tube by an extensive endosalpingiosis of endometrial type. The injection mass escaped into the cavities of this tissue but did not reach the lumen of the tube beyond the site of ligation. Serial sections, aided by the injection demonstrated the origin of this endometrial tissue from a sprout of the tubal mucosa arising from the tubal stump.

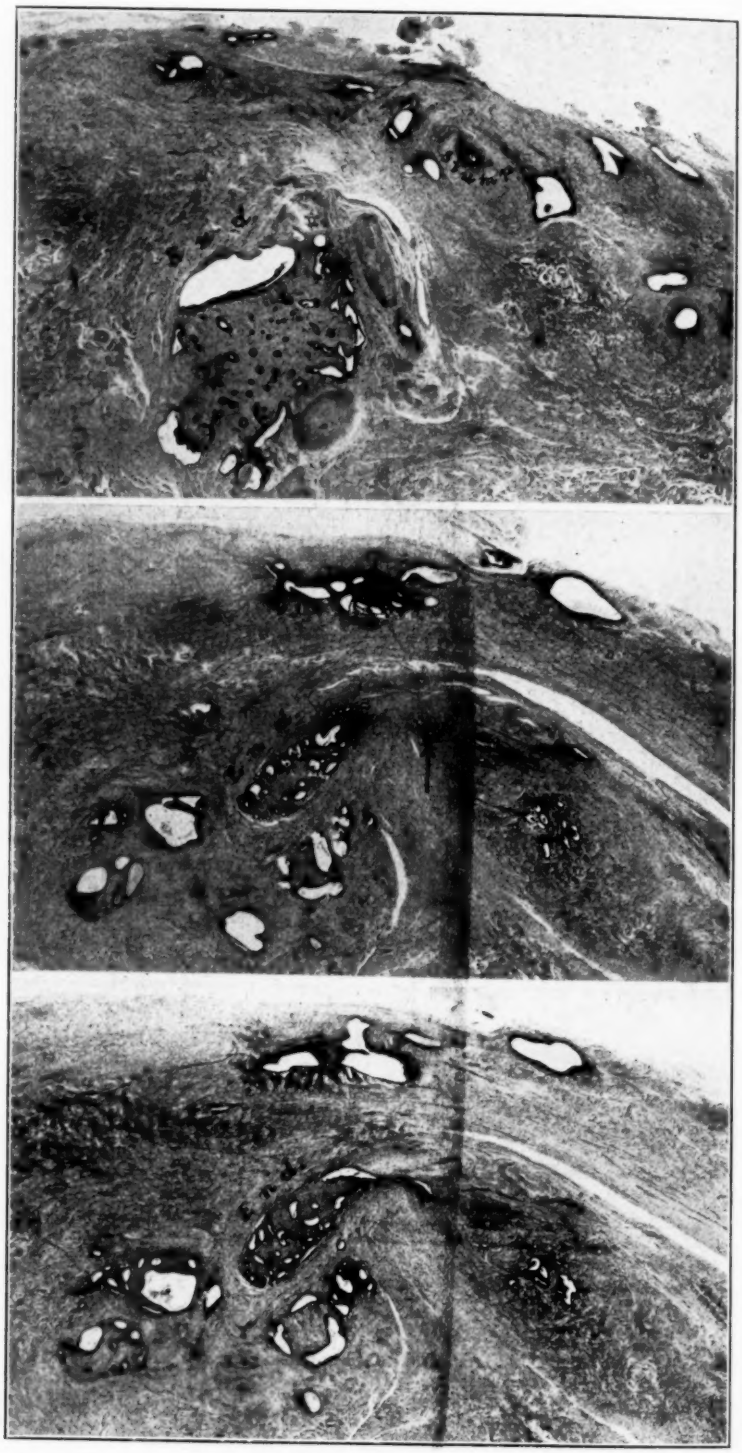

Fig. 14.

The origin of the seedlings, which have a histologic structure identical with that of the sprouts, can never be proved. Some undoubtedly are of nonoperative origin as in patients with a preexisting peritoneal endometriosis. Others, I am convinced, arise from the operation. If they spring from the tubal mucosa the seedlings must come either from the growth of tubal epithelium transplanted in the field of operation, or some of the near-by ones may originally have been sprouts whose connection with the tubal mucosa was "choked off" by the reaction and growth of the surrounding tissue.

From the histologic study of tubal stumps we may draw the following conclusions as to the fate of the tubal mucosa traumatized during salpingectomy and tubal sterilization and the part it plays in the etiology of the misplaced müllerian mucosa so often found in and about these stumps.

1. The "nubbin" of the tube, distal to the ligature applied about the stump, sometimes sloughs away and is absorbed. In other instances it is severed from the tube and lives with or without the development of endosalpingiosis in its wall. Circumstantial evidence (the stump with a stricture situated where the ligature is usually placed) indicates that the entire "nubbin" or the greater portion of it often lives and remains attached to the rest of the stump (Figs. 8, 9 and 10). Endosalpingiosis is apt to arise either in the "nubbin" itself or in the stump proximal to the situation of the ligature. Very often it apparently arises from the tubal mucosa traumatized by the ligature. Endosalpingiosis in a stump proximal to the apparent site of the ligature may have been present at the time of the salpingectomy or have arisen from the repair following the application of a clamp to the stump during the operation.

2. Endosalpingiosis in the uterine cornu of patients who have had a tube removed at a previous operation may or may not be of operative origin. When it arises from the direct outgrowth of tubal mucosa from the end of the severed interstitial portion of the tube it is of

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Fig. 14.—Three photomicrographs (×8) from a series of sections of the left uterine cornu. A left salpingo-oöphorectomy, suspension of the uterus and appendicectomy was done March 4, 1924, by the writer for an adherent retroflexed uterus with endometriosis of the left ovary and culdesac in a patient greatly desiring to have children. The patient had twins a year later and was very badly torn in childbirth. Indications for the second operation were endometriosis and the injuries of childbirth. At the second operation, January 5, 1929, the peritoneal endometriosis was found to be much more extensive than at the first operation. The uterus, right tube and ovary were removed and the pelvic floor repaired. The uterine cavity was injected with gelatin and lampblack. In the upper photomicrograph, the end of the buried tubal stump can be seen containing lampblack with misplaced müllerian tissue about it. To the left and below the stump is a mass of typical endometrial tissue, the cavities of which also contain lampblack. By serial sections and with the aid of the injection mass it was found that a terminal sprout in the form of a small tubule (see arrow of the middle photomicrograph) had arisen from the mucosa of the stump and "expanded" (see lower photomicrograph) into the müllerian mucosa on both sides of it. Some of the injection mass, introduced into the uterine cavity through the cervix, escaped through the lumen of the tubal stump, thence through the sprout into the cavities of some of the misplaced endometrial tissue in the wall of the uterine cornu. The epithelium of the sprout was derived from that of the tube, and the epithelium lining the cavities of the misplaced endometrial tissue (indicated by *End*) was continuous with that of the sprout.

What was the origin of this ectopic endometrial tissue in the uterine cornu? I believe that it arose from a sprout of tubal mucosa.

operative origin (Fig. 14). When it arises from the interstitial portion of the tube, proximal to the end of the stump, it may be either of operative or nonoperative origin.

In the majority of the cases the endosalpingiosis is confined to the tubal stump or, if it extends beyond the same, it invades the tissues of the broad ligament or the uterine cornu depending upon the type of salpingectomy. In other instances it invades other structures which become adherent to the stump. The latter constitutes the most interesting and important group.

In six cases some portion of the intestinal tract became adherent to the stump and was invaded by sprouts arising in the stump. In two

Fig. 15.—Uterus with tubal stump adherent to the head of the cecum (×2/3); endosalpingiosis of the tubal stump and of the wall of cecum. Twenty-two years before the last operation the appendix and right tube and ovary had been removed for a "pus appendix." The indication for the last operation was an extensive postoperative hernia. On opening the abdominal cavity the stump of the tube was found adherent to the head of the cecum lateral to one of its longitudinal bands and therefore not at the appendicectomy scar. Both the end of the stump and the adherent wall of the cecum were indurated and nodular presenting the gross picture of an endosalpingiosis. The tubal stump with a small "shaving" of the thickened wall of the cecum (Fig. 16) were removed and the hernia repaired.

of these the cecum was adherent to the stump of the right tube causing an evident endosalpingiosis of its wall, which was definitely proved by histologic examination in each case (Figs. 15, 16, 17 and 18). In two others the sigmoid was adherent to the stump of the left tube with gross evidence of endosalpingiosis in its wall—not proved by microscopic examination. In two additional cases the omentum was adherent to the uterine cornu and it was invaded by tubules from the tubal stump.

In four cases an ovary was invaded by sprouts from a tubal stump causing an endosalpingiosis of that organ with the development of an "endometrial" hematoma or cyst. Three of these cases were reported in the first and the other in this paper (Case 1, see Figs. 19, 20, 21 and 22).

In three cases an endosalpingiosis was present in the abdominal wall following ventrofixation of the uterus with tubal sterilization. Two of these were reported in the first communication and the other in this paper (Case 2, see Figs. 23, 24 and 25). The endosalpingiosis in all three was shown to have arisen from sprouts invading the abdominal wall from the tubal stump.

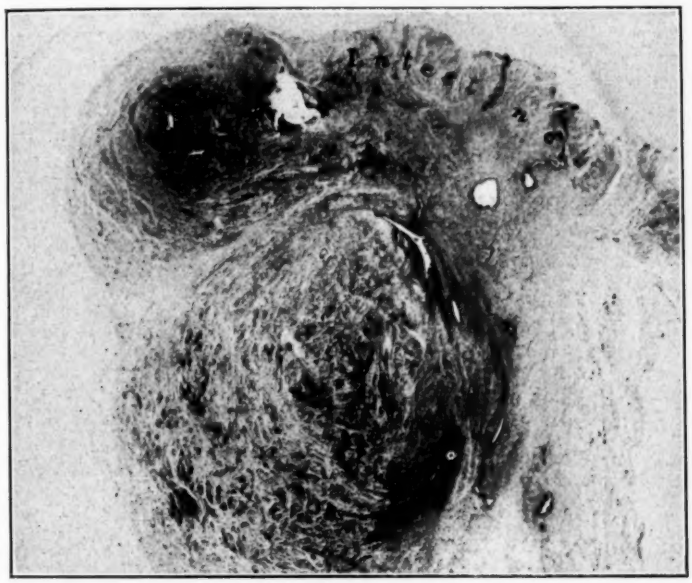

Fig. 16.—Photomicrograph (×10) of a longitudinal section of a portion of the tubal stump showing an endosalpingiosis of the end of the stump with direct extension of its tubules (sprouts) into the wall of the cecum.

Of even greater clinical importance were two ectopic pregnancies, one of which apparently developed in a sprout about the site of an attempted tubal sterilization and the other in the interstitial portion of the tube following salpingectomy with burial of the stump in the uterine cornu. The original operation was done by me in both cases.

In several instances slight peritoneal "endometriosis" was present about the site of the salpingectomy or tubal sterilization. In eight patients an extensive peritoneal endometriosis was present. It is difficult to determine the etiology of the endometriosis in this latter group. In some it was undoubtedly present at the original operation. In others it might have been of operative origin.

A detailed report of two of the more interesting cases follows.

CASE 1.—Hemorrhagic cyst of the left ovary with peritoneal endometriosis (the cavity of the ovarian cyst communicated with the lumen of the tubal stump through a terminal sprout of the latter), following resection of the tubes for "fibrosum nodosum" and attempted tubal or tubo-uterine anastomosis. Patient aged 45 (no children, possible miscarriage four years ago) was operated upon March 15, 1910, for sterility. The uterus was retroverted and both tubes were occluded near the uterus by a nodule designated in the operation report as "fibrosum nodosum." According to the description of the operation the "horns of uterus were incised, part of each tube containing fibroid incised down to part of good lumen in tubes and sutured to incised uterus." The uterus was suspended, kidney fixed, appendix not removed. It was difficult to reconcile the description of the first operation with the findings at the last. I wrote to the surgeon who performed the first operation, sending him a copy of the hospital record of his operation and my own findings. He kindly replied, stating that the nodules must have been excised and tubes implanted in the uterine cornua.

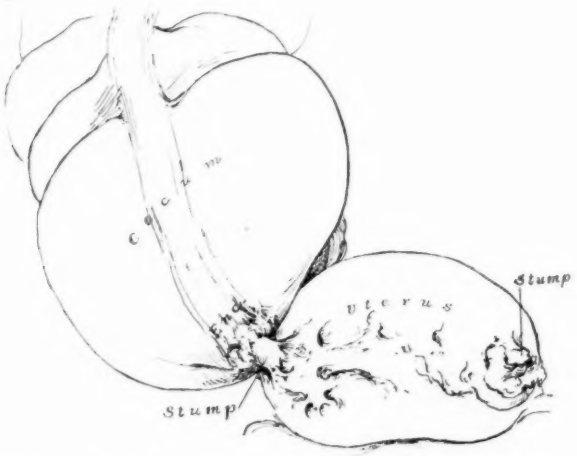

Fig. 17.—Uterus with tubal stump adherent to the head of the cecum (×2/3): endosalpingiosis of the stump and of the wall of the cecum. Ten years before the last operation, both tubes were removed for "salpingitis." The indication for the second operation was pelvic pain. The stump of the right tube was adherent to the head of the cecum possibly at the site of the appendicectomy. The cecum was indurated and nodular at this place, presenting the gross appearance of an endosalpingiosis. The stump was severed close to the cecum; the uterus and right ovary were removed. A small "shaving" of the thickened wall of the cecum was later excised without exposing its mucosa. The uterine cavity was injected with gelatin and lampblack; the mass escaped through the ends of both tubal stumps.

I first saw the patient November 22, 1928. She complained of pain and pressure sensations in the pelvis. Menstruation was regular, normal, and without pain. The uterus was irregularly enlarged and fixed in the pelvis. A preoperative diagnosis was made of an adherent multinodular myomatous uterus. At operation, November 26, the uterus containing multiple myomata was found to be retroflexed and firmly adherent to the bottom of the posterior culdesac. The appendix was first removed. The uterus was freed with great difficulty and in doing so a hematoma of the left ovary was ruptured, a small amount of chocolate-like fluid escaping. I then noticed that the wall of the ovarian hematoma was fused with the posterior surface of the left uterine cornu. Great care was taken not to disturb this relation. The entire uterus and both tubes and ovaries were removed. Peritoneal endometriosis was present on the surfaces of the structures surrounding the left ovary, such as the posterior layer of the left broad ligament, the posterior surface

of the uterus, the left lateral surface of the rectosigmoid and the under surface of a pedunculated myoma. The myoma arose from the fundus of the uterus and, like a "lid," covered the left ovary to which it was adherent. The endometriosis was restricted to the structures just mentioned. The uterine cavity was injected with gelatine containing bismuth subcarbonate. The injection mass freely escaped through the abdominal ostium of the right tube. It did not escape through the

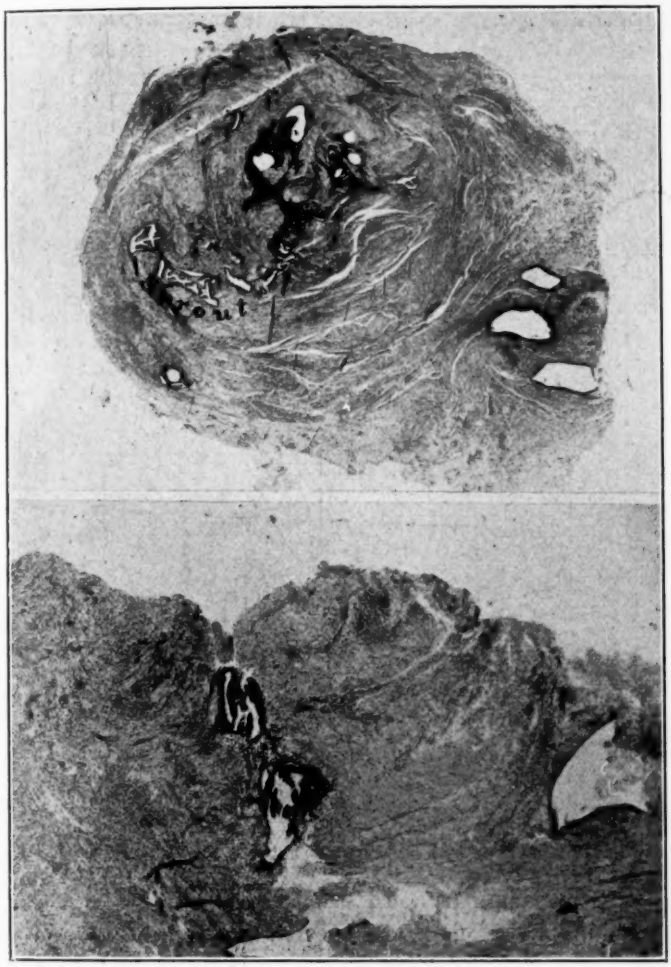

Fig. 18.—Two photomicrographs, the upper of a cross-section of the tube near its attachment to the cecum (×10) and the other (×25) of the small piece of the thickened wall of the cecum, which had been excised. Sprouts arising from the mucosa of the stump are shown in the upper photomicrograph. The invasion of the wall of the cecum by müllerian tissue of uterine type is shown in the lower. Endosalpingiosis of uterine type was present in the left tubal stump.

abdominal ostium of the left tube but passed readily into the cavity of the ovarian hematoma, the wall of which was fused with the left uterine cornu (Fig. 19). In this way we were able to demonstrate that the right tube was patent and the previous operation on this side had been successful. On the other hand, the left tube was not patent and the uterine cavity communicated with that of the ovarian

hematoma through some sort of a fistulous tract. Sections of the right uterine cornu showed that this tube was patent and I was unable to detect the site of repair. Serial sections were made, in a plane at right angles to the long axis of the uterus, of the left uterine cornu and the portion of the left ovary fused with it. We found that the end of the severed tube was not continuous with the tubal stump (Fig. 20). A sprout had arisen from the end of the latter and had invaded the ovary, thus establishing a communication between the lumen of the tubal stump and the cavity of the ovarian hematoma and permitting the injection mass to escape from the uterine cavity into that of the hematoma (Figs. 19, 20, and 21). The epithelial lining of the sprout arose from that of the tube and the epithelial lining of the ovarian hematoma about the opening of the sprout was continuous with that of the latter. Typical endometrial tissue was not found in the lining of the

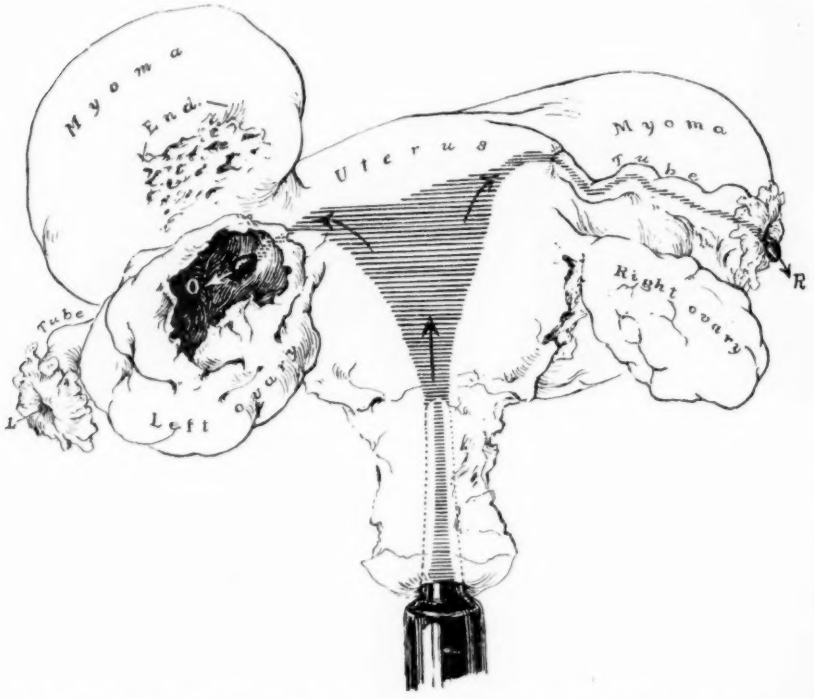

Fig. 19.—Posterior view (×2/3) of the uterus, tubes and ovaries (case 1). Hemorrhagic cyst of the left ovary with peritoneal endometriosis (cavity of cyst communicating with the lumen of the left tubal stump through a terminal sprout of the latter), following resection of the tubes and attempted tubal or tubouterine anastomosis (see case report). Peritoneal endometriosis was restricted to the structures surrounding the left ovary. In freeing the latter the wall of a hemorrhagic cyst was ruptured and its chocolate-like contents escaped. The pedunculated myoma arising from the left uterine cornu was adherent to the wall of the cyst. Endometriosis was present on this surface of the myoma. On injecting the uterine cavity, through the cervix, the mass easily escaped through the patent right tube but did not escape through the left tube. However, it passed readily into the cavity of the hemorrhagic cyst, the wall of which was fused with the left uterine cornu. (See Figs. 20 and 21).

ovarian hematoma. For the most part an epithelial layer was absent, as so often occurs in hematomas of this type. When present it was similar to that of the sprout arising from the tubal stump. This case is one of four encountered in this series in which a hematoma of the ovary was present, the epithelial lining of which was continuous with the epithelial lining of sprouts arising from a tubal stump. The other three cases were reported in the previous paper. I believe that in all

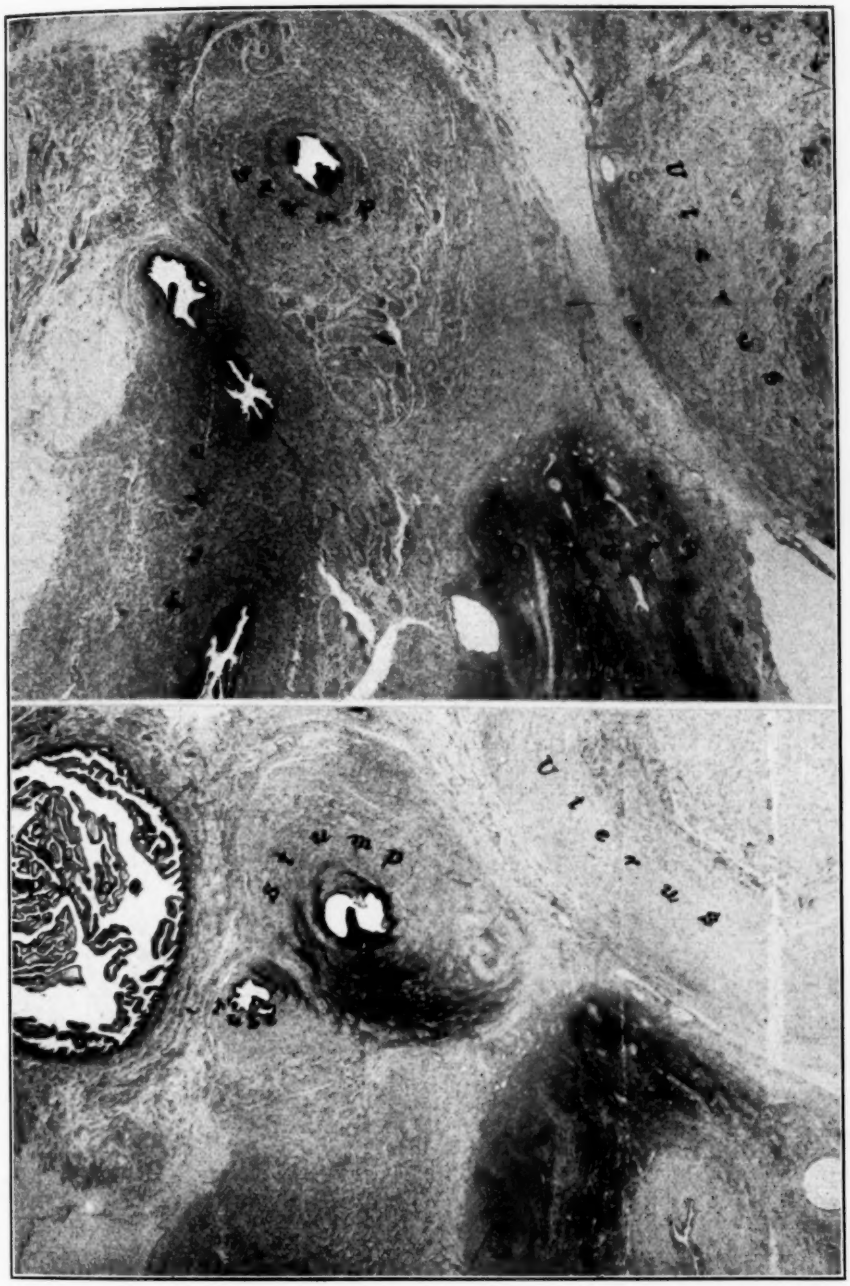

Fig. 20.—Two photomicrographs (×10) from a series of sections through the left uterine cornu with ovary adherent to it (Fig. 19). The stump of the tube with injection mass in its lumen and also the end of the tube without any of the injection mass are clearly shown in the upper photomicrograph. The lower photomicrograph shows the end of the tubal stump nearer the adherent ovary. The end of the resected tube is also shown with indications of the failure of the tubal anastomosis.

four instances the ovarian hematoma (müllerian cyst) developed from tubal epithelium which had invaded the ovary.

What was the origin of the peritoneal endometriosis which was restricted to the structures adherent to and about the left ovary? Circumstantial evidence would indicate that the ovarian hematoma had ruptured, its contents escaping and soiling the pelvic structures which surrounded it. The ovarian hematoma arose from the direct extension of tubal epithelium through the sprout from the tubal stump. Could the peritoneal endometriosis have arisen from the implantation of similar epithelium

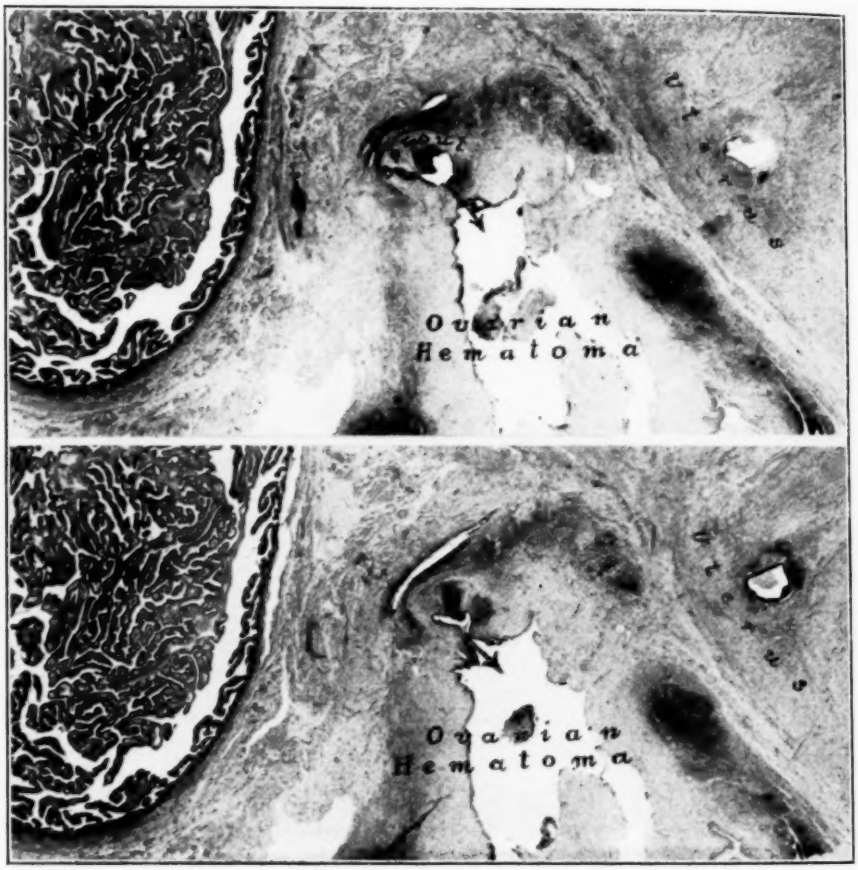

Fig. 21.—Two photomicrographs (×10) from the same series of sections shown in Fig. 20 but at lower levels. A terminal sprout from the tubal stump shown in Fig. 20 has invaded the wall of the ovarian hematoma and in the lower photomicrograph it is shown emptying into the cavity of the hematoma. By these channels the injection mass introduced into the uterine cavity, through the cervix, escaped from that cavity into the cavity of the ovarian hematoma (Fig. 19). The epithelium lining the sprout was derived from the tubal mucosa and the epithelium lining the ovarian hematoma, about the opening of the sprout, was continuous with that of the latter (compare with Fig. 14). What was the origin of the ovarian hematoma?

cast off from the lining of the ovarian hematoma and escaping in its contents at the time of rupture? The histologic structure of the peritoneal lesions (Fig. 22) were even more characteristic of müllerian mucosa than that of the lining of the ovarian hematoma.

CASE 2.—Endosalpingiosis of the abdominal wall about both uterine cornua following tubal sterilization and ventrofixation of the uterus. Patient, aged 37 (two children), had had three operations for the cure of prolapse of the uterus. At the last operation twelve years ago both tubes and ovaries were severed from their uterine attachment and the uterus was drawn through the abdominal incision. The abdominal wall was closed about the uterus at the level of its internal os, leaving the fundus in the subcutaneous portion of the abdominal wall and the tubes and ovaries in the pelvis. She was first seen by me in November, 1928. Her chief complaint was profuse and prolonged menstruation without pain, although the uterus seemed more tender at that time. I did not see her again until September, 1929. The profuse menstruation had continued and the uterus in the abdominal wall beneath the skin annoyed her more than it had in the past and the tenderness during menstruation had increased. On September 30, 1929, the uterus was removed by a supravaginal hysterectomy, the cervix fixed in the abdominal wall, and the pelvic floor repaired. In freeing the fundus of the uterus a hard mass involving both

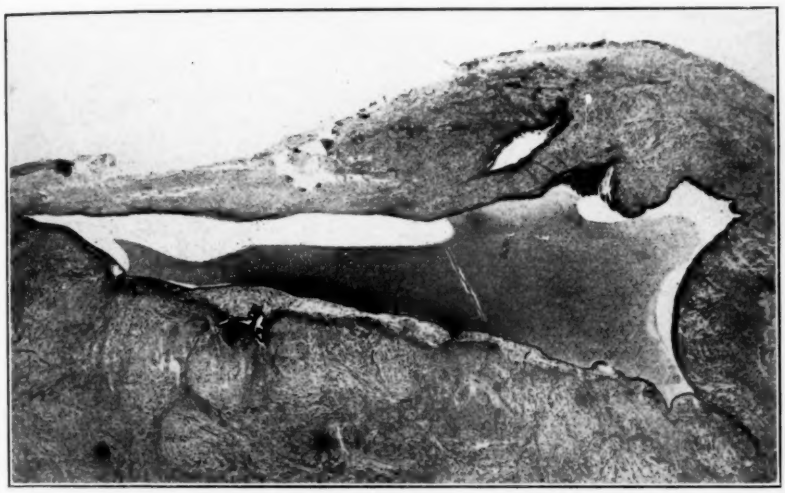

Fig. 22.—Photomicrograph (×8) of a section through the under surface of the myoma, shown in Fig. 19, which was adherent to the left ovary. A typical "endometrial" hematoma is present, occurring in a situation readily soiled by material escaping from the ovarian hematoma beneath it and with circumstantial evidence indicating that the ovarian hematoma had ruptured (see case report). What was the origin of the hematoma shown in this photomicrograph?

uterine cornua and the surrounding adipose tissue was found. These were carefully dissected from the surrounding adipose tissue and removed intact with the uterus (Fig. 23). The uterine cavity was injected with gelatin containing graphite and the specimen hardened in formalin. Sections of both uterine cornua with attached nodules were cut in planes at right angles to the long axis of the uterus. An endosalpingiosis was present in both nodules, the tubules of which had invaded the adipose tissue of the abdominal wall. As the sections of the right side were cut the injection mass was easily seen with the naked eye in the lumina of the müllerian tubules about the tubal stump. As more sections were cut one could see the injected tubules unite and "flow" into the lumen of the stump (Fig. 24). In this way the origin of the endosalpingiosis about the right uterine cornu was definitely determined—namely from sprouts of tubal mucosa in the form of tubules, invading the surrounding adipose tissue. In addition a definite seedling was present in the adipose tissue of the right side (Fig. 23).

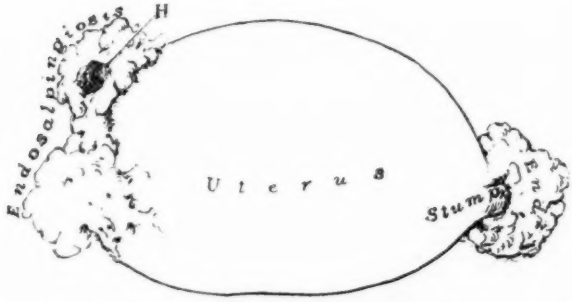

Fig. 23.—Fundus of the uterus (×2/3) with endosalpingiosis of the abdominal wall about both uterine cornua following tubal sterilization and ventrofixation of the uterus (case 2). Adipose tissue invaded by ectopic müllerian tissue is present about both uterine cornua. A seedling marked "H" is present on the right side. The uterine cavity was injected with gelatin and graphite (see Figs. 24 and 25).

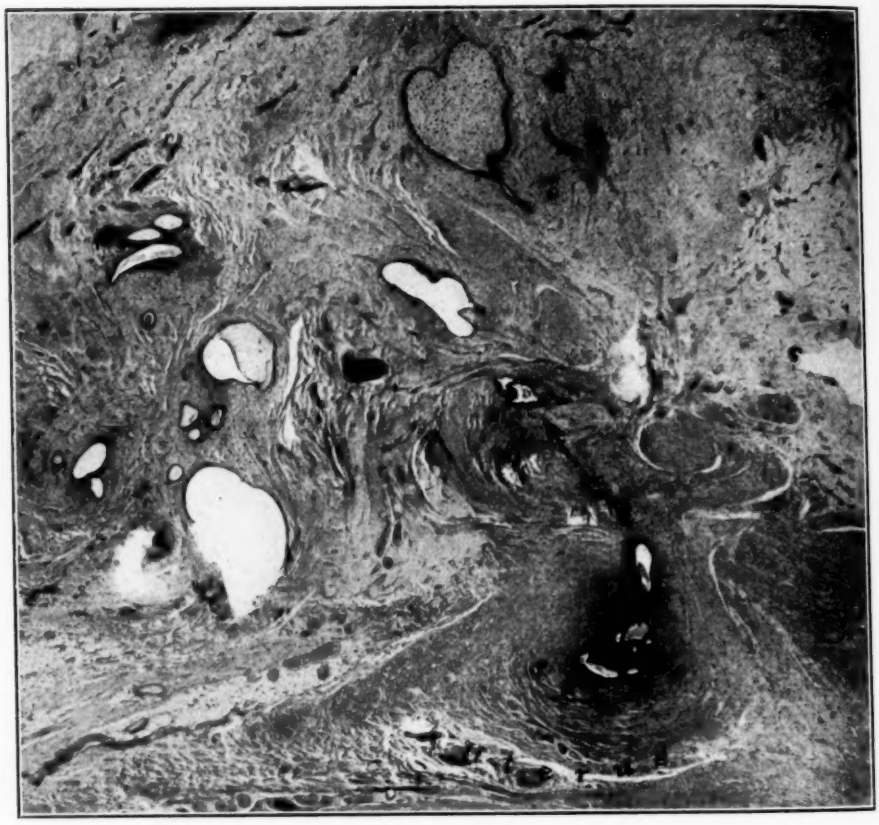

Fig. 24.—Photomicrograph (×10) of one of a series of sections of the right tubal stump with the nodule adherent to it. Graphite was found in the lumina of some of the tubules of the abdominal wall beyond the stump. As more sections were cut the injected tubules united and joined the mucosa of the stump. The origin of the endosalpingiosis about this stump was definitely determined—namely from sprouts of tubal mucosa invading the surrounding adipose tissue.

On sectioning the left uterine cornu, with its attached nodule, a similar endosalpingiosis was found but without the presence of the injection mass in the lumen of any of its tubules. The end of the tubal stump was closed by "normal healing." Endosalpingiosis was present about the end of the stump (Fig. 25). Circumstantial evidence would indicate that it also must have arisen from tubal mucosa. If by sprouts, their connection with the mucosa of the stump must have been "pinched off" by the contraction of the wall of the stump. On the other hand a "nubbin" of the tubal mucosa may have been tied off at the original operation, the endosalpingiosis thus arising from the growth of this transplanted tubal mucosa.

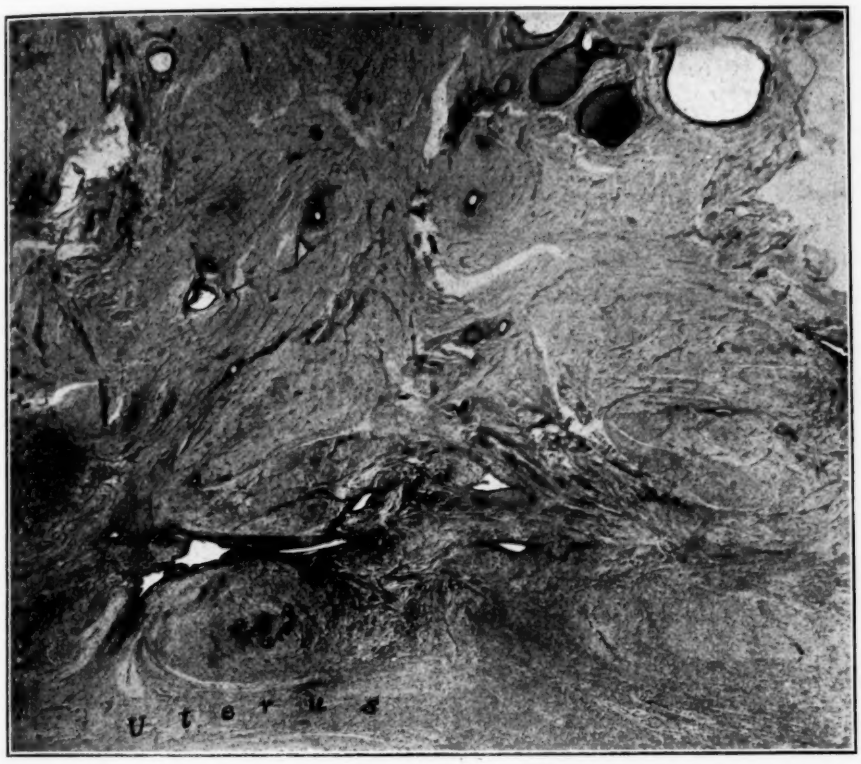

Fig. 25.—Photomicrograph (×10) of one of a series of sections of the left tubal stump and the nodule adherent to it (Fig. 23). Graphite was not found in the lumina of any of the tubules beyond the stump. The end of the stump was closed by "normal healing." Circumstantial evidence would indicate that the endosalpingiosis about this stump also might have arisen from tubal mucosa. If by sprouts, their connection with the mucosa of the stump must have been "pinched off" by the healing of the wall of the stump. On the other hand a "nubbin" of the tubal mucosa may have been tied off at the original operation, the endosalpingiosis thus arising from the growth of this transplanted tubal mucosa.

THE ETIOLOGY OF POSTSALPINGECTOMY ENDOSALPINGIOSIS

In some instances, misplaced müllerian mucosa undoubtedly was present in the uterine portion of the tubes at the time of the original operation. I doubt if its incidence was any greater in the one hundred patients who had a salpingectomy or tubal sterilization than in the

hundred control patients without a previous operation. It was present in 13 per cent of the latter. In the majority of the cases, the endosalpingiosis arose from the overactivity of tubal epithelium in the repair of the salpingectomy wound. This activity is sometimes so great that the sprouts, arising from the traumatized and stimulated mucosa of the stump, may invade the tissues in which the latter is buried or to which it becomes adherent. The type of operation and likewise its occasion apparently are of minor significance in the etiology of the endosalpingiosis as compared with the inherent tendency of tubal epithelium to become invasive when permitted to do so and when properly stimulated. It occurred in all types of salpingectomy which I have had the opportunity to study. I have never obtained a uterine cornu in which the entire interstitial portion of the tube had been excised.

The original operation took place in the gynecologic clinic of the Albany Hospital in only nineteen of the one hundred patients. It was, therefore, impossible to determine the exact technic of the salpingectomy in the majority of the others. We also had difficulty in ascertaining the condition for which the tube or tubes were removed in many patients. We do not know in just how many patients the tube or tubes were removed for salpingitis or its results. These probably constitute a large group. However, the incidence of endosalpingiosis in this group (estimated) was no greater than in patients with tubal sterilization in whom the tubes are apt to be normal. Tubal sterilization had been done in fourteen patients and in eleven of these endosalpingiosis was present, ten bilateral. Bilateral salpingectomy had been done in thirty-three patients, endosalpingiosis was present in twenty-seven and it was bilateral in twenty-one. These figures suggest that the tubal mucosa and its inherent tendency to become invasive are usually the same in both tubes of the same person, though differing in individuals. While endosalpingiosis developed in stumps in which the tube was severed distal to the uterus it appeared to be more frequent in stumps near the uterus or buried in the uterine cornu, the usual situation of endosalpingiosis of nonoperative origin. Possibly the tubal mucosa in these situations "naturally" has a greater tendency to become invasive when the opportunity presents itself. A stump close to the uterus or in the uterine cornu would probably have a better blood supply than one distal to the uterus. The burial of the stump would also increase the blood supply to its tissues and enhance the growth of the tubal mucosa. The growth of tubal epithelium initiated by operative injury, would be maintained by three factors, removal of restraint (damage to tissues surrounding the mucosa and relative tardiness in its repair), preservation of blood supply and the presence of specific stimulation. For the latter we look to the ovaries. The salpingectomy had been done in

all of the patients before the menopause. Both ovaries had been removed in only two patients. Endosalpingiosis was not present in the tubal stumps (four in number) of these patients, but they are too few in number to be of any statistical value.

ENDOSALPINGIOSIS FOLLOWING TORSION OF THE TUBE

If endosalpingiosis arises in the repair of a large percentage of the tubal stumps of operative origin why should it not also occur in the repair of stumps resulting from amputation of tubes by torsion? The last three years we have been on the lookout for tubal stumps of non-operative origin and have encountered four cases.

CASE 3.—Patient aged 33 years. Operation at the Albany Hospital, September 20, 1927. The uterus was retroverted, drawn to the right with its cornu firmly adherent to the side of the pelvis. Right tube and ovary were absent, left tube and ovary appeared normal. In attempting to free the uterine cornu a structure adherent to it and resembling the ovarian vessels was severed. This proved to be the right ureter. The injury was repaired by an end-in-end anastomosis. The right uterine cornu was excised, appendix removed, and uterus suspended. The patient made an uneventful recovery. An endosalpingiosis of tubal type was present in the tubal stump. From the circumstantial evidence found at operation, it would appear that the right tube and ovary had been amputated by torsion and subsequently were absorbed.

CASE 4.—Patient aged 59 years, operation at the Albany Hospital, September 12, 1929. A cyst of the right ovary (size of a large grapefruit) was found densely adherent to the side of the pelvis, uterus and other pelvic structures. The distal portion of the right tube was absent (at least I was unable to find it). The tubal stump, club shaped and about 2.5 cm. long, was present. The uterus, ovarian cyst, opposite tube and ovary, and appendix were removed. The patient made an uneventful recovery. An endosalpingiosis of tubal type was present in the tubal stump. The uterine end of the opposite tube was normal. From circumstantial evidence, found at operation, it would appear that there had been a torsion of the pedicle of the cyst with amputation of the tube.

CASE 5.—Patient aged 42 years, operation at the Albany Hospital, December 10, 1929. A large myomatous uterus, filling the pelvis and extending into the abdominal cavity, was present. The left tube and ovary were jammed between the tumor and the pelvic brim. After ligating and cutting the left ovarian vessels the uterus was lifted out of the pelvis. I then noticed that the left tube was twisted and had been almost completely severed in its midportion. The uterus, left tube and ovary and appendix were removed. The patient made an uneventful recovery. An endosalpingiosis of tubal type was present in the traumatized portion of the left tube.

CASE 6.—Patient aged 27 years. Operation at the Albany Hospital, February 10, 1930. Multiple small myomata were present. The right ovary was absent and the greater portion of the right tube, a stump about 2 cm. long being present. There were no adhesions and the ovarian vessels of the right side could not be found. The opposite tube and ovary appeared normal. The appendix, myomata and tubal stump were removed. The patient made an uneventful recovery. Endosalpingiosis was not present in the tubal stump. The lack of adhesions and my inability to find the ovarian vessels on the right side led me to believe that the absence of the right ovary and tube might have been of congenital origin.

These cases are too few in number to enable us to determine the frequency of endosalpingiosis arising from the repair of injury to tubes following torsion. However, they suggest that the repair following torsion is similar to that following operative removal.

ENDOMETRIOSIS FOLLOWING SUBTOTAL HYSTERECTOMY AND HYSTEROTOMY

In the repair of salpingectomy wounds, tubal epithelium frequently invades the wall of the stump and at times any organ or structure becoming adherent to it. What is the behavior of the uterine epithelium in the repair of the uterine stump after subtotal hysterectomy and also in the healing of incisions through the uterine wall?

Primary endometriosis, arising from the invasion of the uterine wall by its mucosa is not of infrequent occurrence. In subtotal hysterectomy the uterus is frequently cut across above the internal os, thus leaving in the stump a portion of the body of the uterus with its endometrium. We would expect the uterine epithelium sometimes to invade the stump and any structure becoming adherent to it just as tubal epithelium invades the stump of salpingectomy wounds. I have been looking for it and have encountered only one instance. In this case the cervix was fixed in the pelvis by a tumor mass causing the patient great discomfort. The cervix and mass were removed through an abdominal incision. It proved to be an extensive endometriosis (so-called adenomyoma), arising from the mucosa of the hysterectomy stump. I wrote to the surgeon who removed the uterus and he claimed that there was no evidence of an endometriosis in the uterus removed.

If the endometrial tissue in laparotomy scars, after the incision of the pregnant uterus, develops from bits of uterine mucosa transplanted by the surgeon we should expect often to find a similar condition in the uterine scar and in near-by pelvic structures following these operations. Schwarz[12] reports that in his study of the cesarean scar of the human uterus he found endometrial tissue along the line of incision in two instances. In his experimental study of the cesarean scar in the guinea pig, endometrial tissue was found in several cases along the line of incision as well as on the peritoneal surface of the uterus. I have had the opportunity to study only two cesarean scars and one hysterectomy scar following an incision in the nonpregnant uterus. Misplaced uterine mucosa was not found in these cases. J. Whitridge Williams[13] made the following statement to me in a recent personal communication on the healing of cesarean scars: "I have had an abundant opportunity of studying the cesarean scar. Without going into my records, I shall say that I have at least fifty such specimens. In no instance do I recall any invasion of the scar by aberrant mucosa, though in many cases a tongue of mucosa extends into the inner side of the scar. This I take it is due to imperfect suturing and not at all to any invasive property."

The frequency of aberrant mucosa in salpingectomy scars as compared with the infrequency of aberrant mucosa in cesarean scars admits of two possible interpretations, either tubal epithelium is more invasive than uterine or else pregnancy lessens the activity of the uterine epithelium.

Only four patients in this series were operated upon primarily for tubal pregnancy. Endosalpingiosis was found in only one of the four stumps. It was not present in the uterine portion of the opposite tube in this case. I have encountered four instances of tubal pregnancy in nonoperated tubes with an endosalpingiosis in the uterine portion of the tube. Therefore, I am unable to estimate the influence of pregnancy on the growth of tubal epithelium stimulated by operative injury.

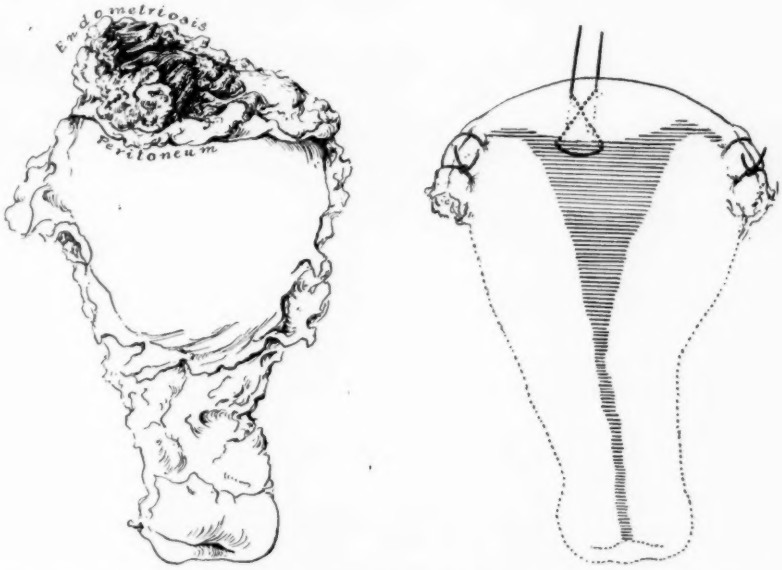

Fig. 26.—Endometriosis of the abdominal wall, from tubules arising from the uterine mucosa, following ventrofixation of the uterus. Anterior view of the uterus (×2/3) with endometrial nodule excised from the abdominal wall and attached to the fundus (case 7). Sketch to the right indicates the burial of the tubal stumps in the uterine cornua at the first operation and the figure eight traction suture of catgut, the ends of which were rethreaded and passed through the recti muscles in the closure of the abdominal incision. I believe that this traction suture must have penetrated the uterine cavity and caused a rent in the uterine wall which later was filled with the uterine mucosa (Fig. 27). Tubules arising from this uterine mucosa penetrated the wall of the uterus above the rent and invaded the abdominal wall (Fig. 28). Endosalpingiosis of tubal type arising from the buried tubal stumps was present in both uterine cornua but was only of histologic interest.

In 1929 Hosoi and Meeker[14] published a very comprehensive review of the subject of endometriosis and included in it an abstract of 87 cases of endometriosis of the abdominal scar which they had collected from the literature. They state that sections of the uterus in these cases where the fundus was adherent to the tumor or mass in the laparotomy scar did not show any endometrial tubules. This demonstrated "that the laparotomy tumors reported in the literature were

not due to an extension from the uterine cavity." Nicholson[15] in his review of endometrial tumors of laparotomy scars also states that "the anatomic continuity between the epithelium of the uterine mucosa and that of the tumor of the abdominal wall had not been established in a single instance in the cases collected by him."

In my first paper on endosalpingiosis following salpingectomy, two cases of "endometriosis" of the abdominal wall after ventrofixation

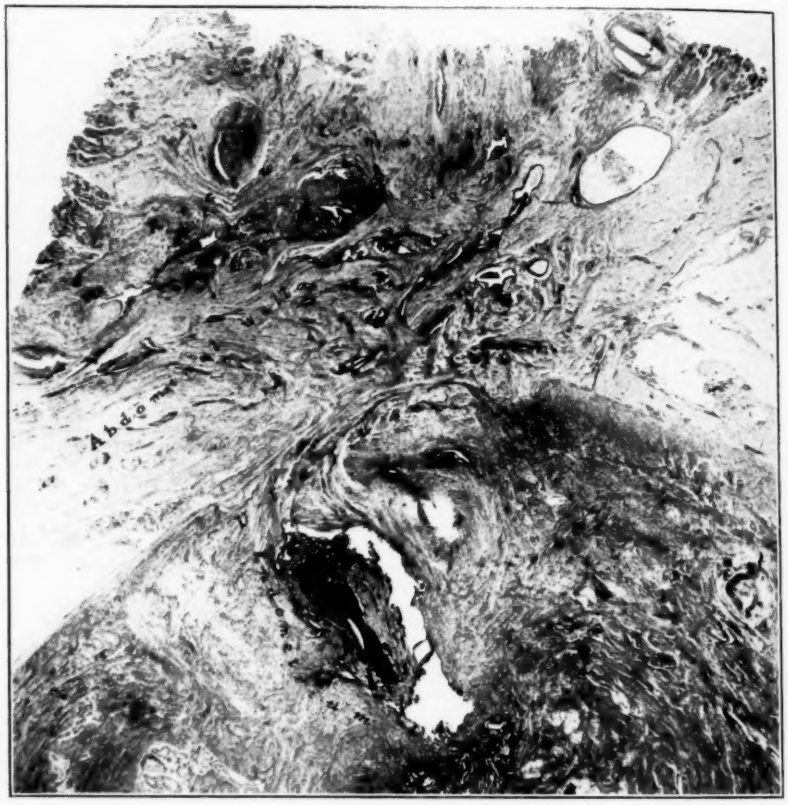

Fig. 27.—Photomicrograph (×6) of one of a series of sections of a portion of the uterine wall with attached nodule excised from the abdominal wall. The rent in the uterus probably caused by the traction suture is filled with endometrium. The portion of the abdominal wall attached to the uterus is infiltrated with tubules (Fig. 28) which have invaded the rectus muscle.

were reported in which it arose from the direct invasion by tubules from the tubal stump (tubal sterilization in one instance and salpingectomy in the other). Since then I have encountered a third case (reported in the present paper).

I have seen only one instance of endometriosis of the abdominal wall after ventrofixation in which it arose from tubules arising from the uterine mucosa.

CASE 7.—The patient aged twenty-eight (one child five years old) was first operated upon by me, November 6, 1924, for a weakened pelvic floor, and adherent retroflexed uterus due to salpingitis. The cervix was cauterized, pelvic floor repaired, appendix, left tube and ovary and right tube removed. The fundus of the uterus was fixed extraperitoneally to the abdominal wall. She was readmitted to the Albany Hospital in November, 1928, with the following history: She was well for a year after her first operation. This was followed by increasing menstrual pain which was felt both in the pelvis and in the abdominal scar. The pain began

Fig. 28.—Photomicrograph (×10) of another section from the same series shown in Fig. 27. A tubule, arising from the uterine mucosa filling the rent, has invaded the uterine wall above the rent (see arrows) and extended into the abdominal wall causing the endometriosis in this situation. On account of the large amount of endometrium filling the rent, the injection mass, introduced into the uterine cavity, was unable to penetrate the tubules arising from it.

with the flow and lasted three or four days. Lately she was forced to spend the greater part of the menstrual period in bed. On pelvic examination the uterus was found to be fixed to the abdominal wall and tender on palpation. At operation, November 8, the right rectus muscle was found to be invaded by a nodule arising from the fundus of the uterus. This was dissected from the muscle and

removed with the uterus (Fig. 26). The cystic right ovary was resected. The patient made an uneventful recovery.

Endosalpingiosis of tubal type, arising from the buried stumps of the interstitial portions of the tubes, was present in both uterine cornua and was of no clinical significance. The endometriosis of the rectus muscle arose from tubules derived from the uterine mucosa (Figs. 27 and 28). The latter had filled a rent in the uterine wall, apparently caused by a traction suture. Tubules arising from this had penetrated the uterine wall above the rent and had invaded the overlying abdominal wall.

For many years it has been my practice, in ventrofixation of the uterus, to pass a figure-of-eight suture of catgut in the wall of the fundus of the uterus, leaving the ends long and use it in place of a tenaculum. The ends of the suture are rethreaded and passed through the deeper structures of the abdominal wall on both sides and tied in the closure of the abdominal incision. I believe that in this instance the needle penetrated the uterine cavity and as traction was made during the operation the uterine wall was torn from within outward. Two errors were committed at the first operation. The first was of judgment in not removing the uterus. The second was of technic in penetrating the uterine cavity with the suture and in passing it to one side of the midline of the uterus. Conditions created at the first operation later caused the patient great pain and discomfort and made necessary a second operation.

Ballin[16] in 1928, published a very interesting paper on menstrual fistulas. Of particular interest are those which communicated with the uterine cavity. He states that over forty cases of this type of fistula had been reported. In one of his cases (Case 3) endometrial tissue was present in the abdominal wall and the fistula passing through this communicated with the cavity of the uterus which was adherent to the abdominal wall at this point. He believes that ventrofixation of the uterus in the presence of pelvic peritonitis seems especially prone to be followed by menstrual fistulas. If the fixation suture penetrates the uterine cavity an excellent chance for a menstrual fistula is created.

THE CLINICAL SIGNIFICANCE OF POSTSALPINGECTOMY ENDOSALPINGIOSIS

Postsalpingectomy endosalpingiosis is often of slight extent and of scientific interest only. When confined to the tubal stump or uterine cornu it is of no more clinical significance than endosalpingiosis of nonoperative origin. When it extends beyond the stump and invades other organs or structures it is liable to cause discomfort to the patient. It is difficult to determine how many of the patients in this series were required to have a second operation solely on account of the extension of the endosalpingiosis beyond the salpingectomy wound. Two of the three patients, with endosalpingiosis of the abdominal wall from the invasion of the recti muscles by tubules from the tubal stump after ventrofixation of the uterus, were operated upon solely for this condition. Three of the four patients with ovarian endosalpingiosis arising from the invasion of the ovaries by sprouts from the tubal stump and likewise three of the four patients with a similar condition of the intestinal wall were operated upon for pain-

ful "adhesions" to which the sprouts from the tubal stump contributed. There were also others in which postsalpingectomy endosalpingiosis added to the adhesions present. In addition there were two instances of pregnancy in the tubal stump, one following salpingo-oöphorectomy of one side, and the other following tubal sterilization. In the above-mentioned cases the necessity for another operation was initiated at the first. Had better judgment been exercised at the first operation or better technic been employed in the salpingectomy or tubal sterilization the indications for a second operation probably would not have arisen. On the basis of the incidence of postoperative endosalpingiosis alone salpingectomy is followed by greater possibilities of discomfort than hysterectomy.

The majority of the patients in this series were operated on again for conditions other than the coexisting misplaced müllerian mucosa in and about the tubal stump. Pain and discomfort, not relieved by conservative surgery for pelvic infection or its results, furnished a large group. There were only two instances of pregnancy in the remaining tube. Seventeen were operated upon for uterine myomata and six for cancer of the uterus. Two of the latter have subsequently died from this disease. In this group there were four cases of cancer of the body of the uterus, one intracervical (accidental finding) and one of the vaginal portion of the cervix which was treated with radium but did not respond favorably. There was only one instance of ovarian carcinoma. Had hysterectomy been done instead of salpingectomy or tubal sterilization at the first operation a second one would not have been necessary in the vast majority of the patients in this series. Aside from the incidence of postsalpingectomy endosalpingiosis, a woman without her uterus has greater assurance of good health and longevity than a woman with it.

The larger number of children born to women who have had one tube and ovary removed is the strongest possible testimony in favor of conservative surgery where subsequent pregnancy is possible. The large number of diseases to which the uterus is heir as well as the incidence of postsalpingectomy endosalpingiosis should warn us to use better judgment in the choice of operation in patients requiring salpingectomy and tubal sterilization. To deprive a woman of the possibility of having children by bilateral salpingectomy or tubal sterilization and often leave a useless uterus, an organ prone to many diseases, frequently has proved to be poor surgical judgment.

I believe it may be stated that if salpingectomy is indicated a hysterectomy should be done, except as follows:

1. In women desiring children or who should have them—when that possibility can be preserved.
2. When hysterectomy adds greatly to the dangers of the operation.
3. When the uterus is used to help support the pelvic floor.

4. In women greatly desiring to keep their uterus and who will be very unhappy if aware that it has been removed.

In our clinic we are very keen to preserve the fertility of women desiring children and always attempt to save ovarian tissue in women, especially those who have not reached the menopause. We err on the side of ovarian conservation. In saving one or both ovaries after hysterectomy we also save the attached tube if normal. It lessens raw areas and better preserves the circulation of the ovary. I have never known of endosalpingiosis arising from the severed end of the tube not removed, but believe it must occur.

Salpingectomy has a very important place in pelvic surgery. What technic should be employed to lessen the incidence of postoperative endosalpingiosis? Our own technic has been either to remove the tube close to the uterus or to excise a wedge-shaped piece of the uterine cornu including some of the interstitial portion of the tube and close the operative wound. Nineteen of the hundred patients were first operated upon by us and endosalpingiosis developed in eleven of these, and in four of the eleven a second operation was required to relieve the patient of conditions resulting from the endosalpingiosis which was initiated at the first. We concluded that our technic had been most favorable for the cultivation and growth of tubal mucosa. Since realizing this (over two years) we have either removed the tube with a cautery or else have cauterized the stump after severing it. We have not had an opportunity to learn the results of this change in technic. Eighty-one of the patients were first operated upon elsewhere. It was impossible to determine the exact technic of the salpingectomy in these cases. In the majority of them the tube was severed distal to the uterus and the stump ligated without attempting to bury it. It is our impression that endosalpingiosis is less likely to develop in this type of operation than in that associated with burial of the stump. On the other hand the four instances of endosalpingiosis of the intestinal wall and three of four cases of endosalpingiosis of the ovary evidently followed this type of salpingectomy. When we consider the danger of pregnancy developing in the tubal stump (two cases) I believe that excision of the interstitial portion of the tube is the operation of choice. Whether or not the cautery is of any real value I cannot say.

In ventrofixation of the uterus care must be exercised not to penetrate the uterine cavity with the fixation suture.

SUMMARY

A very important law governs the healing of operative wounds of hollow viscera and might be stated thus: "The growth of epithelium, initiated by operative injury, is confined to the repair of the lining of the viscus; it does not actually invade the walls of the organ; it ceases to grow when the wound is healed, and, when transplanted in immedi-

ate or remote operative wounds, it does not live. Fortunately this law is generally obeyed. Violations occur but they are infrequent, often transitory and usually insignificant. There is one striking exception to this rule and that is the behavior of tubal epithelium in the repair of salpingectomy wounds. Sprouts of this epithelium often invade the wall of the stump and may extend beyond the latter. It may continue to grow after healing is complete. Seedlings with the same structure as the sprouts occur in both the immediate and remote operative wounds.

Should intestinal epithelium display the same activity in the repair of appendicectomy wounds, as that shown by tubal epithelium in the repair of salpingectomy wounds, the appendix would be removed only for acute inflammatory conditions of that organ. Its removal for "chronic appendicitis" and as a routine procedure in other operations would be discouraged.

Tubal stumps from one hundred patients who had had a previous salpingectomy or tubal sterilization were studied. As bilateral salpingectomy or tubal sterilization was done in forty-seven patients, one hundred and forty-seven stumps were available. Misplaced müllerian mucosa was found in or about one hundred and twelve of these stumps as compared with sixteen instances of misplaced müllerian mucosa in two hundred cornua from one hundred uteri, with intact tubes, which had been removed by operation. Even in fifty uteri with intact tubes removed for the sequelae of salpingitis (a well-recognized cause of endosalpingiosis) misplaced müllerian mucosa was found in nineteen of the one hundred uterine ends of the tubes.

By injecting the uterine cavity with pigmented gelatin the origin of the sprouts from the tubal mucosa, in both the intact tubes and the stumps, can be more easily demonstrated than in the noninjected specimens, and their course followed as readily as the course and branches of an injected blood vessel.

A previous endosalpingiosis was probably present in only a relatively small percentage of the tubal stumps. In the majority of them it arose from the overactivity of tubal epithelium in the repair of the salpingectomy wound. Its incidence was as great in tubal sterilization stumps as those following salpingectomy for salpingitis. The condition for which the tube was removed as well as the usual type of salpingectomy are apparently of minor importance in the etiology of endosalpingiosis as compared with other factors which, at present, are not fully understood.

Postsalpingectomy endosalpingiosis usually arises from sprouts growing out from the traumatized mucosa of the tubal stump. The sprouts may be terminal or lateral. These sprouts may invade not only the wall of the stump but also may extend beyond it, invading the tissues in which it is buried or any organ or structure adherent to

the stump such as the wall of the intestine (four cases), the ovary (four cases), and abdominal wall (three cases). In addition there were two instances of pregnancy in the tubal stump.

The misplaced tubal mucosa in these lesions at times retains its original structure and at other times *assumes the structure and function of the uterine mucosa.* It presents the histologic picture of endometriosis of nonoperative origin.

In the various operative procedures, incident to salpingectomy, bits of tubal and uterine mucosa may be transplanted by the surgeon both in the immediate and remote operative field. Endosalpingiosis with the same histologic structure as the sprouts, is found (as seedlings) in situations where tubal and uterine epithelium might have been sown.

When endosalpingiosis is confined to the tubal stump it is of no more clinical significance than endosalpingiosis of nonoperative origin. When it extends beyond the stump, conditions often arise requiring a second operation. These conditions were initiated at the first operation.

Hysterectomy is followed by fewer complications than salpingectomy. A retained uterus too often requires a second operation for conditions arising in it other than postsalpingectomy endosalpingiosis.

Conservative surgery does not always conserve the health of the patient. It is important to use better judgment in the choice of operation in patients requiring salpingectomy and tubal sterilization, and if hysterectomy is contraindicated, a technic should be employed which will lessen the incidence of postsalpingectomy endosalpingiosis.

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THE OVARIAN AND PITUITARY CHANGES ASSOCIATED WITH HYDATIDIFORM MOLE AND CHORIOEPITHELIOMA

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SINCE the publication of Marchand's classical paper[1] in 1898, it has been known that hydatidiform mole and chorioepithelioma are often associated with the presence of characteristic ovarian changes which have become known as multiple lutein cysts, or, by some, as "hyperreactio luteinalis polycystica." Indeed, the statement has been generally made, and accepted, that this interesting ovarian lesion has never been observed except with choriomatous disease of the two types above mentioned. This generalization, as we shall see, no longer holds good, for at least one case has been observed in the absence of pregnancy.

In the thirty-two years since the first description of these ovarian changes, it would seem that some definite conclusion might have been reached with regard to their nature and significance, but this is not the case. In extenuation it should be borne in mind that hydatidiform mole is quite infrequent, and chorioepithelioma exceedingly rare. Moreover, the former is ordinarily treated conservatively, so that there is no opportunity to study the ovaries histologically except in the minority of cases in which their complete or partial removal is called for.

Again, it may be added that most of the reported studies upon multiple lutein cysts of this type were published when our knowledge of the histology and physiology of the ovary, still very incomplete, was really quite rudimentary. Many of the statements made, and the theories advanced, in these earlier papers are transparently incorrect when reviewed today. On the other hand, the accurate histological descriptions of many of the earlier writers upon this subject, when interpreted in the light of the more recent advances in our knowledge, constitute contributions of genuine value.

CLINICAL CHARACTERISTICS

As this paper is not primarily a clinical one, only brief reference need be made to some of the clinical characteristics of multiple lutein cysts.

Incidence.—There are not many statistics as to the frequency of association of multiple lutein cysts with choriomatous lesions. The figures most frequently quoted are those of Runge,[2] who found, among 144 cases, that no note of the condition of the ovaries was made in 63; in 24, the ovaries were described as more or less cystic; in 11, palpa-

tion is said to have indicated no demonstrable change; and in 28 no cystic changes were found at operation. Cottalorda's study[3] showed lutein cysts to be present in 59 per cent of the cases of hydatidiform mole, and in 9.4 per cent of those of chorioepithelioma. The incidence of the ovarian changes with hydatidiform mole was found by Krömer[4] to be exactly that given by Cottalorda; i.e., 59 per cent, while Patellani[5] likewise estimated it at between 50 and 60 per cent.

There is much reason to question the accuracy of such statistics. They refer to cases in which there is a definite polycystic condition of the ovary, easily demonstrable at operation or palpable on pelvic examination, but they can hardly be considered an index of the incidence of lesions which, while equally characteristic, are not demonstrable except by careful histologic examination. The presence or absence of these characteristic ovarian changes cannot always be determined by palpation alone. As we shall emphasize later, very characteristic "hyperreactio luteinalis" may occur with ovaries which are little or not at all larger than normal. Such changes may be discoverable only on histologic examination, and this is only occasionally possible, for the reason that laparotomy is not often indicated in hydatidiform mole, by far the more frequent of the two causative lesions.

The second reason for doubting the accuracy of such statistics as those quoted above lies in the fact that the character and degree of ovarian change probably differ according to the stage of the intrauterine lesion, and, to add to the confusion, this relation does not appear to be a chronologically parallel one. For example, in Penkert's case[6] there was present in the uterus a normal embryo, the placenta showing only a small microscopic area of hydatidiform disease. Clinically there had been no vaginal bleeding whatsoever up to the time of the operation. And yet the latter disclosed perfectly characteristic, bilateral multiple lutein cysts as large as a child's head.

One of the two cases recently reported by Fruhinsholz[7] is of very similar type, illustrating the possibility of occurrence of marked ovarian changes with only microscopic hydatidiform changes in the placenta. In other cases, again, there appears to be a definite relation between the stage of the disease and the degree of ovarian change. In the case of Joseph and Rabau (Case IV of their series[8]) no ovarian tumor was present at the first operation, but at the second, done six weeks later, the right ovary was described as being the size of a hen's egg. In Herold's carefully observed case,[9] again, the ovaries, after removal of a hydatidiform mole, were the size of walnuts; six weeks later one was as large as the fist; three weeks later, when the operation was performed, this ovary had reached the size of a man's head, though the other ovary was still only as large as a walnut. On the other hand, I have, in a number of instances, seen enormous hydatidiform moles in which no enlargement of the ovaries could be made out by palpation.

As a matter of fact, there are some, like Santi,[10] who believe that it is really the expulsion or evacuation of the cysts which gives the impetus to their growth. Penkert quotes Runge and Schmorl as having found lutein cysts in the ovaries two years after the expulsion of a hydatidiform mole. This, however, is certainly not the rule, as we shall later discuss.

Such divergent observations as have been mentioned only emphasize the incompleteness of our knowledge as to the exact relationships involved. We believe it to be highly probable that some degree of luteal hyperreaction takes place in every case of hydatidiform mole or chorioepithelioma, and that, were it possible to study each case in its day-to-day development, a greater or less degree of gross polycystic change would be demonstrable in the ovaries. The variations actually observed are not understandable because we know so little of the cause of the chorionic disease and of the pathologic physiology involved in the ovarian response to them. Certain newer additions to our knowledge, which will be discussed in this paper, give promise of throwing light on this problem.

Gross Characteristics of the Multiple Lutein Cysts.—In the most striking cases, the ovarian cysts may reach enormous size and may give rise to troublesome pressure symptoms. In Herold's case, for example, they are described as of the size of a man's head, while in other cases the ovaries may show little or no gross enlargement, although quite characteristic microscopic changes may be present. All gradations between the extremes mentioned may be noted.

Where the ovaries are large and polycystic there is a tendency to preserve the original ovoid ovarian contour, but the surface is apt to be more or less lobulated. The individual cysts are of varying size, with thin walls, while the ovarian stroma is commonly quite edematous. The walls of the cyst are smooth and usually of a yellowish tinge. The contained fluid is most often clear and of amber tinge, but in some locules is either blood-tinged or outspokenly bloody.

In cases in which the ovarian response is less pronounced, the gross changes are quite inconspicuous, and the ovaries may show little or no enlargement under these conditions. Such differences, as already mentioned, may be due to the stage at which the condition comes under observation. The corpus luteum of pregnancy may be detectable on the surface, but is often revealed only on section of the ovary. Some degree of cystic change is practically always seen, and the cysts may show the characteristics already described for the larger, genuinely polycystic ovaries.

Course of the Ovarian Lesions.—While observations on this point are not unanimous, certainly there can be little doubt that spontaneous retrogression and disappearance of the ovarian lesion is the rule after removal of the hydatidiform mole or chorioepithelioma. Mention has

already been made of the fact that some authors have noted the ovarian enlargement only after evacuation of the mole, but even in these cases there is little doubt that this is only temporary, and that it is ordinarily followed by spontaneous disappearance. Mathes,[11] Gouilloud,[12] Lehmann,[13] and others have reported instances of this type. Only recently, Fruhinsholz[7] has recorded two such cases. It is only in the occasional case, where the tumors by their size give rise to troublesome pressure symptoms or incarceration, that their removal may be indicated, as in the cases of Schröder[14] and Stoeckel.[15]

MICROSCOPIC CHARACTERISTICS OF THE OVARIAN LESIONS, WITH ESPECIAL REFERENCE TO THE ORIGIN OF THE LUTEIN CELLS

During normal pregnancy there is noted in the ovaries an increase in the process of atresia folliculi. Moreover, in the later stages there is often seen a striking hypertrophy of the theca interna cells, which assume an alveolar arrangement, and often invade the stroma in large irregular masses. It is these theca lutein cells which are looked upon as the analogues, in the human female, of the cells of Leydig in the testis, and which are therefore often spoken of as the interstitial cells of the ovary, although we do not know of any very convincing evidence on this point.

Certainly these theca lutein cells are not morphologically comparable to the granulosa lutein cells of the corpus luteum. They resemble much more closely the so-called paralutein cells seen in many corpora lutea, which is not surprising when one considers that their histogenesis is identical with that of the latter.

The microscopic picture of the ovarian lesions associated with hydatidiform mole or chorioepithelioma is quite varied, not only in different cases but often in different parts of the same ovary. The degree and the stage of the condition are probably chiefly responsible for the individual differences observed. The earlier studies on the subject, such as those of Wallart[16] and Seitz,[17] indicated that the lutein cells observed in the walls of the cysts are of thecal origin. In other words, there is not only an exaggeration of the process of atresia, with the production of many large follicle cysts, but the theca interna cells undergo a striking lutein transformation.

That this view is correct as regards some cases admits of very little doubt. In our Case 2, for example, there is no question that the lutein cells are derived from this source. Although numerous blocks were examined, the picture is everywhere fairly uniform. The lutein cells are seen in the walls of atretic follicles far advanced toward obliteration, occurring as clumps and strips beneath a heavy layer of cicatricial tissue. No trace of granulosa is to be seen, nor does it seem possible that a granulosa origin can be attributed to any of the lutein areas to be found. It seems that theca cells which had long been lying

dormant were awakened to activity by the exaggerated stimulus emanating, directly or indirectly, from the abnormal trophoblastic overgrowth. It is not strange that the picture of lutein cells apparently strewn throughout the stroma was interpreted by some of the early writers (Schaller and Pförringer[18]) as representing a malignant process of lutein cell origin.

On the other hand, our Case 3 presents a totally different picture. In this case the ovaries showed only slight enlargement, and none of the cysts exceeded 1 cm. in diameter. In many of them the lutein layer is unquestionably of granulosa origin. Indeed, the transition can be readily demonstrated, for in some places the basal layers consist of still unchanged granulosa cells, while the remainder of the granulosa has undergone definite luteinization. The significance of such pictures in relation to the underlying cause is considerable, for, as we shall see, it is just such pictures which may be produced in the ovary after implantation of anterior pituitary tissue, by the methods of Smith and Engle,[19] or Zondek and Aschheim.[20]

The fact that the lutein layer in this case is derived from the granulosa is further indicated by the fact that it is subjoined by another layer of hypertrophied cells, representing the theca lutein layer. This is separated from the granulosa lutein layer by a sharply marked "basement membrane." In other words, in this case the hyperluteinizing process involves both granulosa and theca, just as it does after anterior pituitary implantations or injections.

The degree of luteinization differs in various cysts, and many, indeed, show no such change at all. In some an unchanged or perhaps atrophic granulosa may be seen, while in others the cyst wall may be devoid of any epithelial lining at all, as with the ordinary atretic follicles in normal ovaries. It would seem that only at certain stages is the atretic follicle susceptible to the stimulus involved. In some follicles, again, the granulosa lutein cells are present only in patches or strips, an atypical distribution to which attention has been called by Meyer.[21]

CAUSE AND SIGNIFICANCE OF THE OVARIAN CHANGES

The cause of hydatidiform mole is still unknown, while that of chorioepithelioma is just as much a mystery as that of other forms of malignant disease. With regard to the former, many theories have been advanced, the majority attributing the disease either to inflammatory or other lesions of the endometrium, others to some defect in the ovum itself. The subject is closely linked with the cause of the associated ovarian lesions. Some have urged that the hydatidiform mole is the result of the ovarian disease, while a larger number consider the characteristic ovarian changes secondary to the hydatidiform disease. Pick[22] and Fraenkel[23] were early champions of the first

theory. The latter, who first established the importance of the corpus luteum in early gestation, maintained that the interference with the corpus luteum of pregnancy produced by the polycystic ovarian lesion results in the hydatidiform degeneration of the villi.

The majority of investigators, however, hold to the view that the ovarian changes represent a characteristic response to the exaggerated trophoblastic stimulus associated with choriomatous tumors. This, for example, is the view accepted by Stoeckel,[15] Wallart,[16] Seitz[17] and many others. Still others, among more recent writers, hold to this explanation in more or less modified form. Among these may be mentioned Penkert,[6] Lahm,[24] and Schröder.[14]

The latter advances a viewpoint which, while speculative, is highly interesting. He believes that the factor which normally inhibits follicular activity in early pregnancy is the growing embryo itself. With hydatidiform mole this inhibitory factor is absent, possibly because of the chorionic disease. As a consequence, all stages of follicular activity may be seen. Whereas, for example, in the normal sex cycle, only one, or at most two, corpora lutea of the same age are to be found, with hydatidiform mole, all stages may be observed. In short, he attributes to the loss of this normal inhibition, and to the factor of hyperemia, the production of the ovarian changes. As already stated, this explanation is speculative, and, furthermore, it is almost certainly incorrect, in the light of more recent developments.

A great light has been thrown upon this problem by the recent epoch-making studies of Zondek and Aschheim[20] in Germany, and Smith and Engle[19] in this country, upon the relation of the anterior pituitary to the function of the ovary. We shall not review this work here, as it has already been epitomized by one of us (Novak) in a recent paper.[25] Suffice it to say that the characteristic changes produced in the ovary by the anterior pituitary principles consist of hyperluteinization, hyperemia, and, under certain conditions, exaggerated follicle activity designated as superovulation. The pictures of the hyperluteinization produced in this way must at once suggest a similarity to those seen in certain cases of chorioma, such as, for example, our Case 3.

This analogy has already been urged by Aschheim[26] and Fels,[27] and there can be little doubt of its correctness. A study of the work of Evans and Long,[28] Smith and Engle,[19] and Zondek and Aschheim[20] indicates the varied results produced by the anterior pituitary upon the ovary, depending upon the technic of administration, the dosage and other such factors. Similar variations are seen in the ovaries with hydatidiform mole or chorioepithelioma. Further light is thrown upon this problem by the investigations of Evans and Simpson,[29] which indicate that there are two hormones produced by the anterior pituitary, one of which they designate as a growth hormone, the other as a

maturity-provoking principle. Variations in the proportion of these, they suggest, explain variations in the ovarian pictures produced.

In the main, however, the experimental studies just quoted must suggest that the "hyperreactio luteinalis" associated with chorioma-tous tumors is the result of an exaggerated activity of the anterior pituitary. Aschheim[26] believes that in normal pregnancy the pituitary secretes a growth hormone of importance to the fetus, and that, in hydatidiform mole, where no fetus is present, an excess of this growth hormone exerts its influence upon the ovary. This, however, would not explain such cases as that of Penkert, in which a normal embryo was present with a microscopic mole, but in which marked ovarian changes were seen.

Greater interest attaches to Aschheim's report[26] of a case of hydatidiform mole, with still unchanged ovaries, in which large amounts of anterior pituitary hormone were found in the blood, urine, and also in the fluid of the hydatidiform vesicles. A similar case is reported by Fels.[27] An injection of 0.5 c.c. of the vesicle fluid in this case produced the typical pituitary effects in test animals. Similar results have been reported by both Fels and Aschheim in cases of chorio-epithelioma. Fels suggests, therefore, that the trophoblast is responsible for the increased amount of anterior pituitary in the blood stream. Rössler[30] has reported a series of cases in which this biological method has been used in a quantitative way, as a means of differentiating between normal pregnancy, hydatidiform mole and chorioepithelioma, although his results need confirmation before they can be accepted. He suggests, moreover, and with much logic, that pregnancy tests should prove valuable in determining the completeness or incompleteness of removal of hydatidiform tissue, or, for that matter, of retained chorionic tissue in cases of abortion. In a very recent paper by Schultze-Rhonhof[31] a group of cases is reported in which this test has been applied and found of great diagnostic and prognostic value.

In none of the cases reported by Aschheim or Fels, or, for that matter, in no case as yet reported in the literature, except one, has there been an opportunity of examining the pituitary gland itself. The only case, so far as we have been able to find, in which the histology of the pituitary has been studied, is one reported very briefly by Rössler.[30] In this case the patient died of chorioepithelioma, with extensive metastases. The autopsy showed enlargement of the anterior lobe, with a predominance of eosinophile cells, and wide blood vessels. On the anterior margin there was a heavy distribution of the basophile and eosinophile elements. He concludes that the changes suggest those seen in the hypophysis of pregnancy, though not in complete form. It must be remembered, however, that the patient lived a long time, at least a year and a half, after the extirpation of the chorio-

epitheliomatous uterus. Incidentally, it is of interest to note that the pregnancy test was still positive one and a half years after the operation.

The fact which gives interest and importance to our Case 4 is that a complete autopsy made the pituitary gland available for histological study. Before discussing the relations between the ovarian and pituitary changes, a brief report will be given of the 4 cases which supplied the incentive for this study.

REPORT OF FOUR CASES

The material upon which this study is based consists of 2 cases of chorioepithelioma and 2 of hydatidiform mole in which the ovaries, as well as the intrauterine lesion, were available for study. This is a by no means small material, especially when one considers the extreme rarity of chorioepithelioma. As a matter of fact, comparatively few of the reports in the literature have been based upon the study of more than a single case. Among the 2 cases of chorioepithelioma in our group, there is one of especial interest, because, as already stated, an opportunity was afforded to study the changes in the pituitary gland in association with this disease. The importance of this observation lies in the fact that within the past year or two evidence has been accumulating to indicate that the anterior pituitary lobe, so important in the physiology of the normal sex cycle, is probably an important factor in the production of the multiple lutein cysts under discussion in this paper. This case, incidentally, presents many other points of clinical and pathologic interest, but these have been discussed in a separate paper.[32]

CASE 1.—The tissue from this case, with the clinical notes, were sent to one of us (Novak) by a surgeon in a Southern state. The patient, age twenty-four, had had a normal pregnancy four years previously. In April, 1924, she conceived again, the last menstrual date being April 7. There was slight staining for one day toward the end of May, and a recurrence of bleeding for two days early in June. On June 28, free hemorrhage began, but no embryonic tissue was expelled. Examination at this time showed the cervix to be soft but not patulous, the uterus being enlarged to the size of a four months' pregnancy.

The bleeding continuing, evacuation of the uterus was done on July 1. According to the report of the surgeon, a large quantity of "polypoid" tissue was removed, together with a small amount of placental tissue. Being under the impression that the "polypoid" tissue suggested malignancy, the surgeon performed panhysterectomy, with double salpingo-oöphorectomy.

At operation the uterus was found to be about double normal size, and soft in consistency. Both ovaries were "considerably enlarged," and contained many small cysts. Some of these were filled with a gelatinous material, some with blood. Blocks of the organs were sent to our laboratory for diagnosis.

The "polypoid" tissue was seen to be, not really polypoid, but grape-like and vesicular, being evidently a typical benign hydatidiform mole. This was confirmed by microscopic examination.

The examination of the ovarian tissue showed it to contain numerous small cysts of the follicular type. Some were lined by more or less degenerated granulosal cells, in others the granulosa had disappeared entirely. In some, however, the

granulosa was fairly well preserved, with large areas of theca lutein cells beneath it, as shown in Fig. 1. In still others, the cyst wall showed a lining, usually several layers thick, of typical lutein cells. The lutein layer was not usually complete, but showed a tendency to a patchy distribution of the cells. The relations of the lutein layer left no doubt of its origin, in these cysts, from the granulosa. A typical corpus luteum of pregnancy was also present. Unfortunately only one block of tissue was available for this examination, as the entire specimen could not be secured.

CASE 2.—This case has been previously reported by one of us (Novak),[33] though from a clinical point of view. She was thirty-four years old and had been married seventeen years, with four children, ranging from twelve to five years. There had been no miscarriages. Menstruation had been normal up to the present illness. On September 1, 1902, when the patient was presumably two and a half months pregnant, she had a profuse hemorrhage lasting fifteen minutes. Following this there was intermittent bleeding until October 10, 1902, when a large mass, weighing

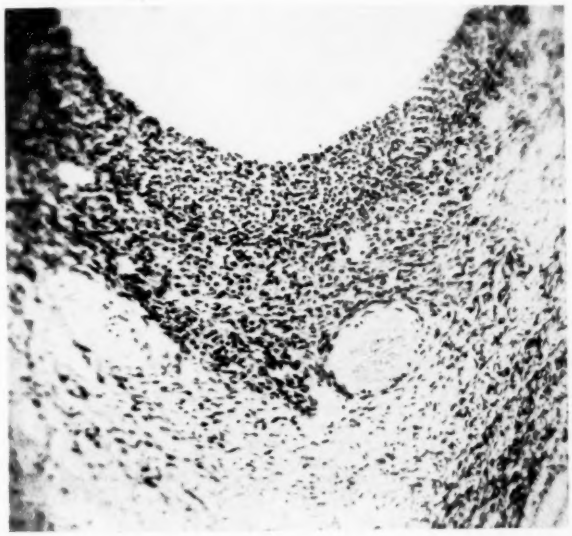

Fig. 1.—Follicle with fairly well preserved granulosa, beneath which is a large patch of theca lutein cells (Case 1), similar to those often seen in normal pregnancy. Other follicles in the same ovary showed no theca lutein change, and in some the granulosa was entirely absent. In still other areas there were follicles lined with typical granulosa lutein cells, giving a picture like that of a corpus luteum in the stage of vascularization.

3 pounds, was expelled. This was described by her physician as "pultaceous." With this, which might have been largely blood clots, there came away a large handful of small vesicles. No fetus was present, though the uterus was enlarged to the level of the umbilicus.

Shortly after this, bleeding recurred, and soon became severe, so that, when she was admitted to the Johns Hopkins Hospital on December 12, the hemoglobin had fallen to 20 per cent. The fundus at this time was three or four times the normal size, and the cervix soft and patulous. A small mass, presumably an ovarian cyst, was palpable in each side of the pelvis. After preliminary building-up treatment, panhysterectomy and double salpingo-oöphorectomy was performed on December 20. The patient made a satisfactory recovery, and was in good health on April 12, 1922, when the last report was received.

The uterus was somewhat larger than normal, and, on being opened, it presented on its anterior wall an elevated area 5 cm. in diameter, which appeared to be covered

by endometrium. Beneath the smooth surface, however, were found many small cysts typical of hydatidiform mole. This was confirmed by the microscope, which showed a hydatidiform mole with marked trophoblastic overgrowth.

The ovaries were much enlarged as a result of multiple cyst formation. The right measured 12 × 7 × 6 cm., the left 9 × 6 × 4 cm. The constituent cysts varied in size, the largest measuring 6 cm., in diameter. Their walls were exceedingly thin and of yellowish hue. The contents were clear and serous in character.

The microscopic picture presented by the ovaries was fairly uniform. The cysts resembled large atretic follicles which in many places had advanced to the stage of obliteration by cicatricial tissue. The granulosa was everywhere absent. Beneath the cicatricial layer, and obviously in the zone of theca interna, could be seen patches

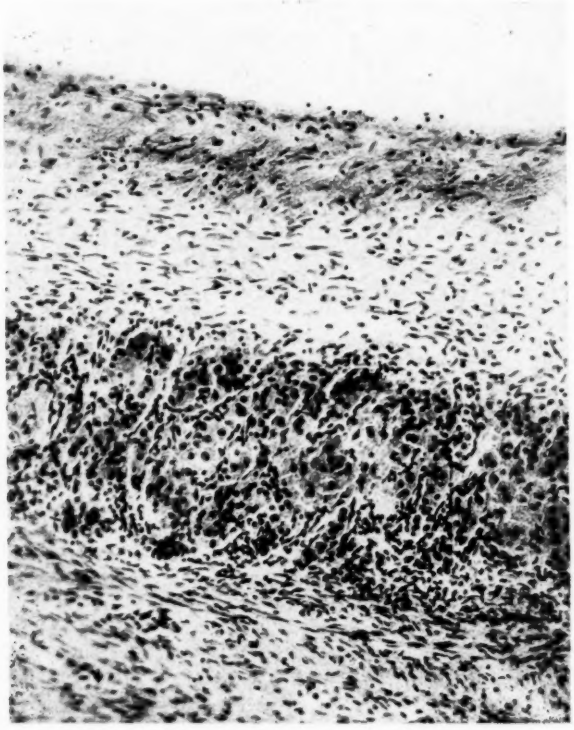

Fig. 2.—A typical field from Case 2, showing a seam of theca lutein cells deep beneath the cicatricial lining of an old atretic follicle. No granulosa, either normal or lutein.zed, could be found in this ovary, although many blocks were made.

and strips of large polyhedral lutein cells (Fig. 2). Here and there they formed a fairly continuous, though thin layer, while in other places only small clumps were to be seen. Even in the depths of long-obliterated atretic follicles such collections could be noted, so that they gave the impression of invading the ovarian stroma. No granulosa was anywhere to be seen, nor did it seem possible to accept any but a thecal origin for the lutein cells in this case. No corpus luteum was found.

CASE 3.—A white woman, age twenty-three, had had a stillbirth at full term in July, 1923. There was considerable bleeding for many weeks afterward, so that a curettage was done in September, and this is said to have been repeated in October and November, because of persistence of the bleeding. There was no

bleeding in December, and the patient had what she thought was a normal period in January, although she bled for two weeks. Hemorrhage recurred on Feb. 22, and continued up to the time she entered St. Agnes' Hospital, in the service of Dr. J. K. B. E. Seegar, to whom we are indebted for the history and the pathologic specimen.

Examination at this time showed the right side of the pelvis to be filled with a tumor mass, pushing the moderately enlarged uterus to the left. The cervix was firm and tightly closed.

A diagnostic curettage was done on March 29, 1924, and a large quantity of tissue, resembling blood clots and placental tissue, was brought away. Microscopic examination showed definite chorioepithelioma.

Laparotomy, on April 5, 1924, showed the uterus to be twice the normal size, and pushed to the left by a large hemorrhagic tumor filling the right side of the pelvis. The tumor mass was apparently intraligamentous and extended out to the pelvic wall. The left side of the pelvis was normal except for adhesions. It was

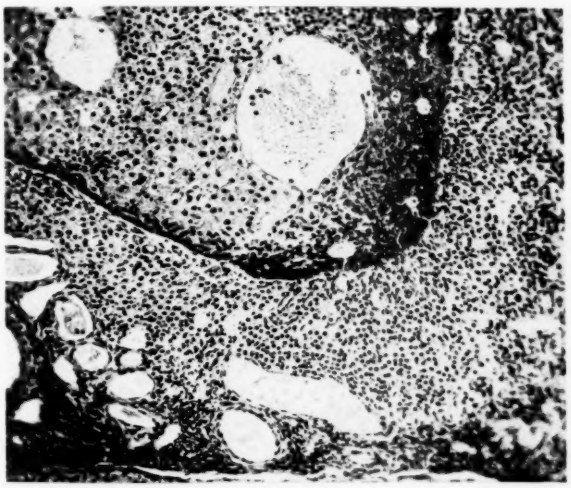

Fig. 3.—This unusual picture, from Case 3, seems to establish that the hyperluteinizing reaction may involve both the granulosa and the theca. The basal layers of the granulosa, seen above, are still unchanged, while the more superficial layers show definite lutein transformation. Beneath the basement membrane is seen the luteinized theca, the cells resembling the theca lutein cells of pregnancy and the paralutein cells often seen in the mature corpus luteum.

impossible to get beyond the right-sided mass, as it extended around and beyond the iliac vessels. A supravaginal hysterectomy was done, and as much of the tumor mass was removed as possible. A number of drains were inserted because of oozing, and the abdomen closed. Death took place on April 25, presumably of extensive metastases to the lung, though autopsy was not obtained.

The pathologic examination showed the uterus to be twice the normal size, and smooth externally. The interior of the uterus was described as of meaty, hemorrhagic appearance, while on the right side the lesion extended into the broad ligament, where it formed a friable, hemorrhagic mass about 10 cm. in diameter. The ovary on this side measured 4 × 3 × 3 cm., its surface showing a few small follicular cysts. On section a large number of similar small cysts were seen, together with a large corpus luteum, evidently in the stage of maturity or beginning retrogression.

On microscopic examination some of the cysts were seen to be ordinary atretic follicles, with no granulosa. Others were lined by a layer of lutein cells resembling

the wall of a corpus luteum in the stage of vascularization. In one or two areas pictures were encountered quite different from any we had hitherto seen in the ovary. The cavity of a few follicles was almost completely filled with cells which in the basal layers were typically granulosal, but which in their upper layers had undergone typical lutein metaplasia (Fig. 3). Their granulosal origin cannot be questioned, especially as the thecal cells are clearly distinguishable beneath the granulosa. Especially interesting is the fact that these thecal cells have undergone lutein transformation, similar to that often seen in pregnancy, and that the granulosal lutein cells are morphologically different from the theca lutein elements. The former resemble the lutein cells of the corpus luteum, the latter the so-called paralutein cells.

This unusual picture, it seems to us, is of vital importance in establishing the fact that the hyperluteinization associated with chorioepithelioma may involve both granulosa and theca, and not, as most authors have believed, only the granulosa or only the theca. It is of interest, also, in that it is similar to certain pictures which have been produced by pituitary implantations or injections, as has already been mentioned.

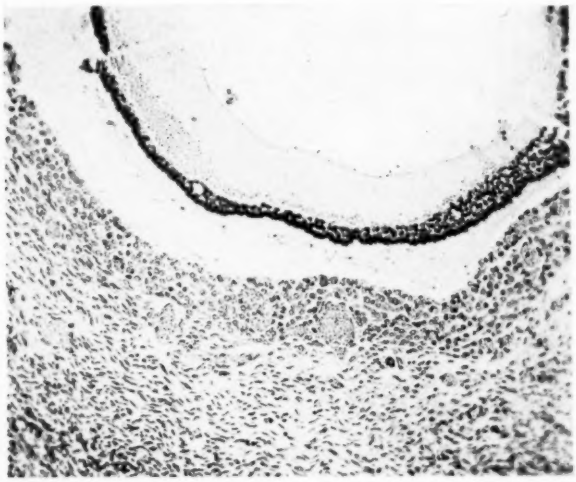

Fig. 4.—Typical theca-lutein changes (Case 4), with degeneration of the granulosa, which is retracted from the theca. Many of the follicles in this case, however, show only the ordinary picture of atresia folliculi.

CASE 4.—The patient, age thirty-one, had been curetted in another hospital on July 13, exactly five months before admission to the Johns Hopkins Hospital. She had had four children. A normal menstruation had occurred on June 16, lasting three days, but bleeding recurred on July 3, continuing up to the time of the curettage on July 13. Numerous small bits of tissue were removed at this operation, although they did not, according to the attending surgeon, suggest placental tissue. The microscopic examination, however, revealed what was considered "retained chorionic tissue."

On November 13 the patient was admitted to the Johns Hopkins Hospital, in the service of Dr. Dandy. She had suffered with such symptoms as headaches and loss of vision for several months, and, without going into details, a diagnosis was made of brain tumor. This was confirmed at operation on November 17. The tumor proved to be a typical chorioepithelioma of the left occipital lobe. The patient died on November 19. The autopsy revealed extensive metastases also

present in the lungs, but the chief point of interest was the fact that the primary tumor in the uterus had entirely disappeared. This interesting case is reported in full in another paper by the present authors.[32]

The ovaries, with which we are more directly concerned in the present connection, showed only slight enlargement, and, on section, presented a considerable number of small cysts. Many of them are simple atretic follicles, usually without a granulosal layer. Others showed a very definite lutein transformation of the theca interna (Fig. 4), while one rather large cyst was lined by a typical lutein layer derived from the granulosa. This is indicated, among other things, by the fact that the theca interna in parts of the same cyst, likewise shows luteinization, the line of demarcation between the two being clearly marked.

The histologic changes in the pituitary were of especial interest, for reasons already mentioned. They are, therefore, discussed below in some detail, with a preliminary consideration of the normal anterior lobe, and some of its physiologic variations.

THE NORMAL HISTOLOGY OF THE ANTERIOR PITUITARY LOBE

In accordance with their size, form, and staining reactions three types of cells may be distinguished in the anterior lobe. Two, because of their affinity for stains, are spoken of as chromophile cells, this group embracing an acidophile or eosinophile variety, and a basophile type. The remaining group, showing no affinity for stains, is represented by the so-called chromophobe cells.

The acidophile cells are polyhedral, with a nearly homogeneous cytoplasm, which is almost filled with coarse acidophilic granules. The nuclei are small, spherical, and stain deeply with hematoxylin.

The basophile cells are somewhat larger, the cytoplasm being filled with coarse basophilic granules, and the nucleus slightly eccentric.

The chromophobe cells are much smaller than the other two types, and not so well outlined. The cytoplasm is scant, and the nucleus round, rather small, and rich in chromatin.

In the human these cells exhibit no very characteristic distribution. The eosinophiles and basophiles show a tendency to form alveoli or cell cords, between which course wide capillaries, with delicate walls. The chromophobes are found chiefly in groups or nests in the centers of these alveoli, and are therefore farthest away from the capillaries. The acidophiles form numerically the largest group.

The most satisfactory staining technic for the study of these cells is that described by Bailey,[34] for use after fixation in either Regaud's solution or formol-Zenker. A modification of Bailey's stain has recently been employed by Kindell,[35] of the Department of Pathology at the Johns Hopkins Medical School. After fixation in either of the two solutions already mentioned, the blocks are imbedded in paraffin, sectioned and stained with acid fuchsin-methyl blue. This differentiates the two types of granules very sharply. The acidophile (alpha) granules stain bright red, the basophilic (beta) granules a deep blue.

There has been considerable difference of opinion as to whether or not the three cell types above described represent merely different

phases of activity in the production of a single secretion. The weight of evidence, however, points to their physiological individuality. This view is urged by Bailey and Davidoff[36] on the basis of their studies upon the eosinophilic adenomata so characteristically found in acromegaly, basophilic granules never being found in hypophyseal adenomas. They therefore feel that the alpha granules represent the secretory product having to do with growth. A similar conclusion as to the individuality of these two types was reached by Smith (P. E.) and Smith (I. B.)[37] from their studies upon the bovine hypophysis, where there is at least a partial histologic separation of the two types. The same view is expressed in the more recent paper of Evans and Simpson,[29] to which further reference will be made below.

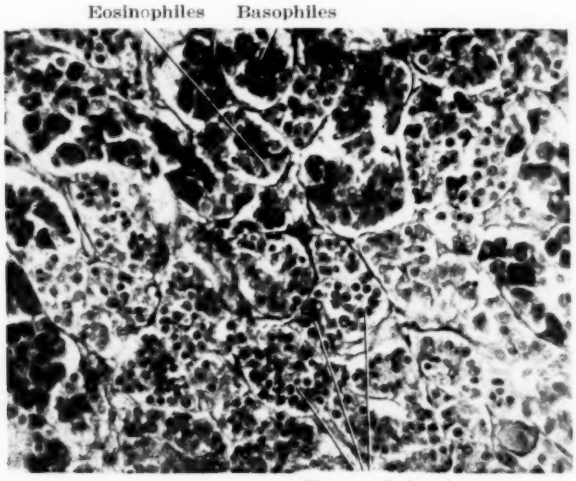

Fig. 5.—Showing the histology of the normal anterior pituitary, with the theca types of cells (see text).

THE PITUITARY AFTER CASTRATION

It is a well-known fact that hypertrophy of the anterior pituitary is one of the results of castration. Engle, moreover, has recently shown that in rats which had been castrated eight months previously, the anterior pituitary yielded a greater amount of the gonad-stimulating hormone than does the normal gland. This was indicated by the premature sex maturation of the animals and by characteristic ovarian changes produced in the latter. Histological examination of the hypophysis in these castrated animals showed a marked increase in the number and size of the basophiles. Intracellular vacuoles, diminishing the amount of cytoplasm, were construed by Engle[38] as representing storage of the hypophyseal sex hormone. Be that as it may, the characteristic increase in the size and number of the basophiles, together with the increase in the physiologic effect upon the ovaries, justify the belief that these cells elaborate the hypophyseal

sex hormone. Corroborative evidence is found in the statement of Rasmussen,[39] that the basophile cells are, in the marmot, more abundant during estrus.

THE PITUITARY IN PREGNANCY

The changes in the human pituitary during pregnancy have been fully studied by Erdheim and Stumme,[40] and have been again described more recently, in another valuable contribution by Erdheim.[41] Increase in size of the hypophysis is the rule in pregnancy, especially in the later stages. This is sometimes so marked as to cause pressure on the optic chiasm, with even such symptoms as partial bilateral hemianopsia. The pronounced enlargement and coarsening of the features in late pregnancy is also presumably of pituitary origin. Similar changes have been described by Cushing[42] in the anterior lobes of the pregnant bitch, cat, and rabbit.

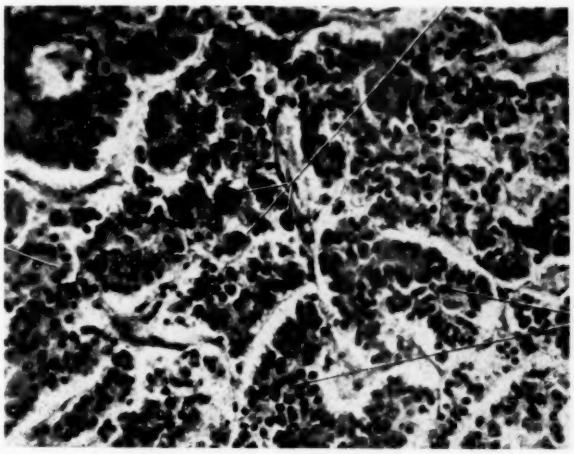

Fig. 6.—The anterior pituitary of pregnancy (seven months). Note especially the increase in size of the cell cords, and the transformation of the chromophobes into the so-called pregnancy cells.

Histologically, the chromophobe cells practically cease to exist as such in pregnancy, being transformed into large cells, with clear and somewhat irregular nuclei (Schwangerschaftzellen). The abundant cytoplasm is filled with fine dust-like granules staining pink with acid fuchsin and eosine. Transitions may be seen between these cells and the eosinophile cells, with their coarser granules. The cells are grouped in broad columns which line the capillary sinuses, crowding out the normally dominant coarsely granular eosinophiles. It is the increase in these modified chromophobes, or pregnancy cells, which is responsible for the enlargement of the anterior lobe. Neither the eosinophiles nor basophiles appear to show any increase or decrease above or below the normal, although usually they are displaced toward the centers of the cell column.

THE PITUITARY IN OUR CASE 4

The histologic changes in the anterior pituitary lobe in our Case 4 need not be detailed, inasmuch as they showed exactly the picture described above as characteristic of pregnancy. It should be emphasized, however, that in our patient the curettage had been performed and the pregnancy terminated at least four months previously, and at a very early stage. The significance of this lies in the fact that, according to Erdheim, within seven weeks after parturition the modified chromophobe cells (Schwangerschaftzellen) return to their normal condition, as observed in the nonpregnant state, although their number may remain larger than before.

As the pituitary in our case, in which the pregnancy was terminated at a very early stage several months previously, still showed changes

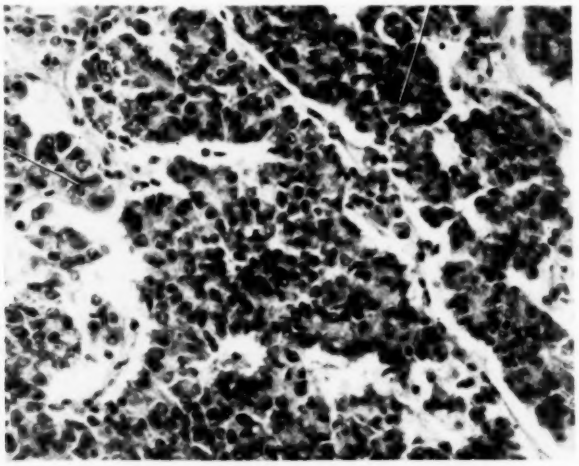

Fig. 7.—The anterior pituitary of our Case IV (chorioepithelioma). The cell cords are even larger than those of the normal pregnancy hypophysis shown in Fig. 6, the other changes being of the same type.

comparable to those of normal full-term pregnancy, it seems probable that the original pituitary response to the abnormal pregnancy was far greater than that occurring in normal gestation. On the other hand, and this is probably a much more important factor, a large amount of trophoblastic tissue was still present in the patient's body, in the form of the cerebral and pulmonary metastases. This view matches up with the biologic studies made by Schultze-Rhonhof in one of his cases of chorioepithelioma. In his patient the pregnancy test was strongly positive one and a half months after total extirpation of the uterine tumor. X-ray examination, however, showed extensive metastases in the lung.

When one considers that in normal pregnancy there is only a relatively slight lutein reaction in the ovary, one must, if the intermediary rôle of the pituitary in producing these changes be accepted, presup-

pose a profound increase of the pituitary hormones to explain the conditions represented by the luteal hyperreaction of hydatidiform mole and chorioepithelioma. The evidence furnished by our own case, together with the studies of Aschheim,[26] Fels[27] and others, already mentioned, indicate that the trophoblast is the normal stimulus to the pituitary. In other words, it seems likely that the ovarian changes may be looked upon as a response to the pituitary hyperfunction, and not directly to the ovum, whether this be normal or abnormal. A rather crucial observation would be to determine whether, in the absence of pregnancy, the pituitary itself can, under any circumstances, call forth changes in the ovary similar to those of hydatidiform mole or chorioepithelioma. Such an observation has actually been reported by Wagner.[43] In this as yet unique case, the patient was operated upon for a pelvic mass, diagnosed as probable extrauterine pregnancy. There had been amenorrhea for four months, although menstruation had been irregular, with frequent amenorrhea, for five years. Incidentally, colostrum was present in the breasts. At operation the uterus was found to be of the size of a six weeks' pregnancy, while both ovaries were the seat of polycystic tumors, typical of those seen with hydatidiform mole or chorioepithelioma. Fearing that there might be an unsuspected chorioepithelioma, Wagner performed a radical operation.

No trace of an embryo was found in the uterus, although the mucosa showed some decidual change and some ectopic decidua was found on the posterior surface of the uterus. The microscopic examination of the ovaries showed typical multiple lutein cysts, with marked increase of granulosa lutein tissue.

The later course of the patient was of great interest and significance, inasmuch as she developed symptoms suggesting a pituitary tumor, and this was confirmed by examination. The tumor was considered to be a benign adenoma, and was treated by the x-ray instead of surgically. This case is interpreted by Wagner as demonstrating that characteristic pregnancy changes in the ovary, or changes similar to those seen with choriomatous tumors, can be provoked by pituitary lesions in the absence of pregnancy.

As bearing on this point, mention may be made of the experiments of Baniecki,[44] who was able to initiate typical pregnancy changes in the anterior hypophyseal lobe of guinea pigs by the injection of placental extracts. This observation would formerly have been difficult to explain, but the recent demonstration by Collip[45] and by Philipp[46] that the placenta yields not only the follicle hormone, but also the anterior pituitary secretion, illuminates it very much. Philipp, indeed, believes that the hormone is produced by the placenta, and that the latter is not merely a storing place for it. He goes so far as to state that the Zondek-Aschheim pregnancy test is really a placental rather

than an anterior pituitary reaction. The whole question is, of course, still quite confused, and many of the reported observations are more or less contradictory. This applies not only to the problem of the anterior pituitary hormone, but also to the older one of the ovarian follicle substance, and of course to the interrelationship of the two. This, however, is not the place for an extensive discussion of these matters.

In the main, the evidence indicates that the anterior pituitary is not only the "motor of the ovary" in its normal cyclical activity, but that it likewise is the direct cause of the ovarian changes of normal pregnancy and of hydatidiform mole and chorioepithelioma. The underlying stimulus of the pituitary, in turn, probably emanates from the trophoblast, although it may apparently, in the light of Wagner's observation, be provoked by primary pituitary lesions.

It is too early to speak of the relative importance in this connection of the two secretions which, according to Evans and Simpson,[29] are produced by the anterior lobe, and it is quite possible that there are individual variations in different cases and in different stages of the same case. If the reliability of the method of separation of the two principles outlined by Evans and Simpson is established, it would seem that the problem will be open to experimental attack. For the present, however, the results of the enormous amount of experimental work of the past two years or so have not been entirely crystallized, and there are still a number of contradictions in the work and views of those studying the problem. These will, no doubt, be eliminated as the work advances. But even now we may accept as established the far-reaching fact that the anterior pituitary is of fundamental importance in the sex cycle, that it exerts its effect through and upon the ovaries, and that it must play a part in the production of such pathologico-physiologic disturbances as those we have been discussing.

SUMMARY

This paper is based upon the study of two cases of hydatidiform mole and two of chorioepithelioma, in all of which the ovaries were available for study, while in one of the cases of chorioepithelioma a histologic study of the pituitary was also possible. The importance of such observations at the present time is especially great, because of recent developments in our knowledge of the physiologic interrelationships between the ovaries and the anterior pituitary. The remarkable "hyperreactio luteinalis" which probably occurs at some stage in every case of hydatidiform mole and chorioepithelioma, but which does not always assume the form of the so-called multiple lutein cysts, is definitely comparable to the ovarian changes which are produced by anterior pituitary implantations or injections. Histologic studies, such as those included in this report, and also the biochemical studies

which have been described by a number of authors, leave little doubt that the anterior pituitary is the immediate cause of the lutein hyperreaction seen in the ovaries of such cases. Our own studies indicate that the hyperluteinization involves both the granulosa and the theca interna.

The histologic study of the anterior pituitary in one of our cases of chorioepithelioma showed an abnormally marked and persisting pregnancy reaction. This observation, for the first time, offers a histologic explanation for the persistence of the pregnancy test long after removal of the primary tumor, as has been reported by two or three recent authors. This abnormally persistent pregnancy reaction in the pituitary, with the persistence of the pregnancy test, is no doubt due to the presence of considerable masses of trophoblastic tissue in the metastases, as was almost certainly the case in our patient. In short, the evidence indicates that the interreaction is a triangular one, the trophoblastic increase being responsible for the pituitary reaction, and the latter, in turn, calling forth the abnormal ovarian response.

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SOME OBSERVATIONS ON THE ETIOLOGY OF DYSFUNCTIONAL UTERINE BLEEDING

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THE present-day conception of the etiology of dysfunctional uterine bleeding ascribes it to a disturbance of pelvic physiology, discarding as obsolete the older theories that related it to a local disease of the uterine wall or endometrium.

The modern theory has been gradually evolved during the last thirty years by Cullen, L. Fraenkel, Hitschmann and Adler, Schroeder, Robert Meyer, Emil Novak, and others, and is being confirmed, though somewhat modified by recent discoveries, in ovarian hormonology. It was first definitely epitomized by Robert Schroeder, who studied the ovaries and endometria of 53 patients hysterectomized for dysfunctional bleeding. His conclusions may briefly be summarized as follows:

The normal phases of the endometrial cycle are induced by two ovarian hormones, widely different and probably antagonistic in their properties. The maturing follicle, through the agency of its growth hormone, governs the first proliferative stage of the endometrial cycle during which the glands become hypertrophied, lengthened and tortuous. Ovulation takes place at a varying time near the middle of the menstrual cycle. The hormone of the newly-formed corpus luteum (corpus granulosum) alters the morphology of the endometrium and transforms it into a secretory organ in preparation for the nidation of the fertilized egg.

If from some defect in the motor impulse (located by Schroeder in the germ plasm of the egg) ovulation does not take place, the graafian follicle persists and no corpus luteum (granulosum) is formed. Consequently, the endometrium, in the absence of the hormone of the corpus luteum, does not undergo the customary premenstrual secretory change; but, under the continued influence of the persisting follicle, acquires an irregular growth commonly called gland hypertrophy or gland hyperplasia. (Since these terms are often misleading, I have adopted in their place the word *dysplasia* as better expressing the incoherent nature of the process.)

Minor defects of ovulation or corpus luteum integrity produce corresponding variations in the endometrium and the menstrual rhythm.

The dysplasia of the endometrium results finally in localized areas of thrombotic necrosis with crumbling of the tissues and consequent hemorrhage.

Schroeder found the foregoing factors constantly present in his 53 cases; namely, absent or defective corpus luteum, persisting follicle or follicles, gland dysplasia, and localized necrosis. His work has not been universally accepted.

The present paper records an attempt to test the theory by a series of personal observations.

I. The first investigation consisted of a repetition of the work of Schroeder. For this purpose I was able to collect the uterus and ovaries of 18 patients who had been subjected to hysterectomy and ablation of the ovaries for severe dysfunctional bleeding. Only those cases were included which were free from fibroid tumors, or from lesions that might produce accidental bleeding.

The cases are abstracted severally and the results tabulated.

HYSTERECTOMY SERIES: DYSFUNCTIONAL BLEEDING

CASE 1.—E. F. Path. No. 15318. Age forty-two. Married, 2 children. Menorrhagia and metrorrhagia, five years. One ovary previously removed. Endometrium: Gland dysplasia. Localized areas of necrosis. Ovary: Several persistent follicles. No corpus luteum. Myometrium: Small round cell infiltration. So-called "metritis."

CASE 2.—L. L. Path. No. 6353. Age twenty-three. Single. Constant metrorrhagia, several years. Two previous curettings. Endometrium: marked "Swiss-cheese" dysplasia. Ovaries: Right, several persistent follicles. Left, small old corpus luteum. Myometrium: Negative.

CASE 3.—M. W. Path. No. 16473. Age fifty-one. Married, 3 children. Metrorrhagia, two years. Endometrium: Gland dysplasia, bizarre. Extravasation of blood. Surface necrosis. Ovaries: Right, involuted corpus luteum turning to albicans. Two persisting follicles. Rich granulosa. Left, persisting follicle cyst with rich granulosa. Myometrium: Hypertrophied.

CASE 4.—A. G. Path. No. 15789. Age forty-eight. Married, 11 children. Menorrhagia and metrorrhagia, 5 years. Endometrium: Gland dysplasia, bizarre, "Swiss-cheese." Areas of blood extravasation, and necrosis. Ovaries: Right, no corpus luteum. Left, no corpus luteum. Several cystic follicles. Myometrium: Hypertrophied.

CASE 5.—K. H. Path. No. 11379. Age forty. Married, 3 children, 2 miscarriages. Prolonged menstruation, but periods regular. Endometrium: Gland dysplasia with marked hyperplasia, and invagination of glands. Extensive local extravasation of blood with necrosis. Ovaries: Right, no corpus luteum. Left, cystic corpus luteum deficient (note periodicity of eta.). Myometrium: Negative.

CASE 6.—M. H. Path. No. 10989. Age forty-one. Married, 7 children. Metrorrhagia, one year. Previous curetting (6 months). Endometrium: Gland dysplasia. All three phases represented. Marked subepithelial hemorrhages. Thrombosis of vessels. Ovaries: Right, follicle cyst. Left, collapsed corpus luteum (7 mm.). Two persisting follicles. Myometrium: Hypertrophied.

CASE 7.—J. B. Path. No. 13729. Age forty-three. Married, 3 children. Severe metrorrhagia, 2 months following skipping. Endometrium: Gland dysplasia. Shaggy, bizarre, dilated glands, mixed types. Some extravasation of blood. Thrombosis of vessels. Ovaries: Right, large follicular cyst. No corpus luteum. Left, old disintegrating corpus luteum (2 months). Myometrium: Great hypertrophy with edema (procidentia).

CASE 8.—E. McG. Path. No. 10751. Age thirty-five. Married, 4 children. Metrorrhagia, 7 months. One ovary previously removed. Endometrium: Gland dysplasia, shaggy, mixed phases, dilated glands. Thickened stroma. Marked extravasation of blood with crumbling. Ovary: (Single.) No corpus luteum. Large cystic follicle. Myometrium: Negative.

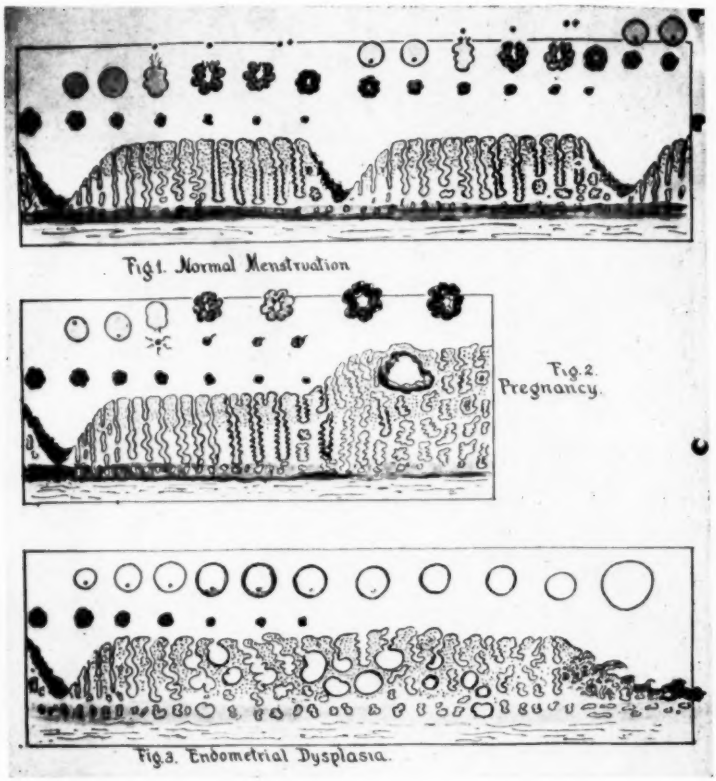

Fig. 1.—Diagram showing the parallelism between the phases of the follicle and endometrium during a normal menstrual cycle. The middle row of diminishing figures indicates the involution of the preceding corpus luteum. The upper row of figures illustrates the development of the graafian follicle. As it develops its hormone produces characteristic growth changes in the endometrium. Near the middle of the cycle the follicle bursts, ejects the egg and becomes a corpus luteum (more accurately called the corpus granulosum, as it is not yellow at first). The corpus granulosum functions up to the 28th day, inducing by means of its special hormone secretory changes in the endometrial glands. The egg, if unfertilized, dies supposedly on the 28th day. With the death of the egg the corpus granulosum begins to degenerate, turns yellow and gradually involutes. The cyclic changes in the endometrial glands are depicted. At first simple tubular structures, the glands become hypertrophied and tortuous under the influence of the growth hormone of the developing follicle. As soon as the corpus granulosum is formed, their structure is altered to that of a secretory organ. The epithelium assumes the beaker-form of secreting cells, and the glands exhibit a saw-toothed (sägeformig) appearance. When the egg dies and the corpus granulosum collapses, the endometrium disintegrates down to the basal layer, crumbles, desquamates, bleeds and rapidly regenerates (menstruation).

Fig. 2.—The ovarian and menstrual cycle in pregnancy. The first part of the cycle is like that of normal menstruation. If the egg is fertilized, the collapse of the corpus granulosum and endometrium does not take place. The corpus granulosum grows larger and continues its hormonic influence on the endometrium. The endometrium persists as a secretory organ, becoming the decidua and retaining as such the characteristics of its premenstrual stage in a more pronounced form.

Fig. 3.—The follicle and endometrium in a typical case of dysfunctional bleeding. The middle row of figures shows the involuting corpus luteum. The top row shows the developing follicle which at the proper time fails to burst, discharge the egg, and become a corpus granulosum (ovulation). The follicle persists and continues to exert by means of its hormone a growth influence on the endometrium. The glands undergo an irregular hypertrophy (dysplasia). In the absence of a corpus granulosum there is no secretory phase. In a typical case menstruation does not take place. The dysplasia of the endometrium results in localized thrombosis and necrosis, with consequent crumbling and hemorrhage. The persistent follicle or follicles become cystic, and either by their own secretion or by that of the pituitary body may maintain the dysplasic condition for an indefinite period. If the endometrium is curetted it usually regenerates in the form of dysplasia.

The diagram represents only a typical case. There may be many variations. For

CASE 9.—M. C. Path. No. 10956. Age thirty-seven. Married, 9 children. Polymenorrhea (2 weeks' intervals, 10 days flow). Endometrium: Gland dysplasia. Mixture of phases. Great hypertrophy of surface epithelium. Dense hypertrophy of stroma. Subepithelial blood extravasation. Ovaries: Right, old disintegrated corpus luteum cyst. Several persisting follicles, one with ovum. Left, very small. No corpus luteum. No follicles. Myometrium: Negative.

CASE 10.—R. K. Path. No. 15252. Age forty-five. Married, 6 children. Metrorrhagia, 6 months. Endometrium: Gland dysplasia. Great variation in thickness of mucosa, mixture of phases. Subepithelial extravasation. Thromboses. Crumbling. Ovaries: Right, small old collapsed corpus luteum, beginning disintegration. Left, old corpus hemorrhagicum. Myometrium: Hypertrophied.

CASE 11.—M. M. Path. No. 14024. Age fifty. Married, 2 children. Metrorrhagia, 3 years. Endometrium: Gland dysplasia in an atrophied mucosa. Thickened stroma. Sclerotic blood vessels. Extravasation and desquamation. Hyper-

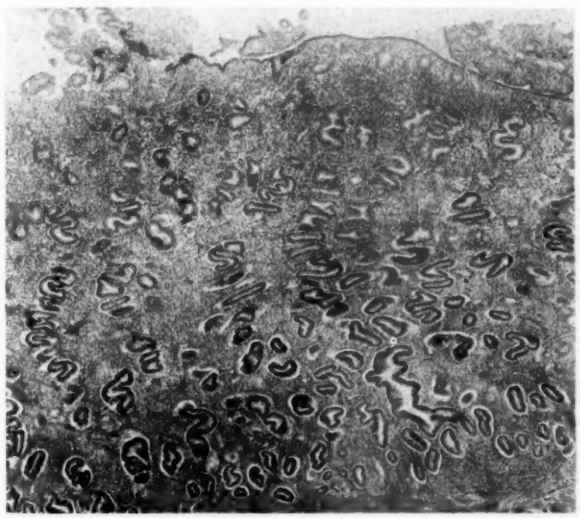

Fig. 4.—Normal proliferative stage of the menstrual cycle. The glands show a uniform growth and tortuosity.

trophy of epithelium. Glands few but hypertrophied. Ovaries: Right, old follicle cyst. No corpus luteum. Left, no corpus luteum. No follicles. Myometrium: Enormous hypertrophy, with edema and arteriosclerosis.

CASE 12.—J. D. Path. No. 16011. Age thirty-three. Married, 2 children. Severe metrorrhagia, 5 months. Menorrhagia (regular), several years. Previous curetting and radium (non-sterilizing dose). Endometrium: Gland dysplasia in mild degree. Glands greatly hypertrophied with branching and dipping into muscularis. Type fairly uniform. General extravasation of blood in stroma. Ovaries: Right, no corpus luteum. No follicles. Left, old corpus luteum with beginning fibrosis. Persistent follicle cysts with rich granulosa. Myometrium: Extremely flaccid but microscopically negative.

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example, ovulation may be incomplete and the corpus granulosum defective. In such a case, the endometrium may be under the influence of both the follicle and the corpus hormones. The menstruation would then be periodic but abnormally profuse or prolonged. The endometrium would show a mixed picture of both proliferative and premenstrual phases. Figs. 1, 2, 3 are adapted from Schroeder.

CASE 13.—K. McL. Path. No. 12625. Age thirty-seven. Married, 1 child. Severe polymenorrhea. Endometrium: Gland dysplasia. Mixed phases in great profusion. Swiss-cheese formation. Extravasation of blood with some surface destruction. Ovaries: Right, small. No corpus luteum. A few cystic follicles. Left, small. No corpus luteum. Myometrium: Negative.

CASE 14.—B. P. G. Path. No. 16135. Age forty-five. Single. Polymenorrhea and metrorrhagia. Endometrium: Gland dysplasia. Swiss-cheese type. Extravasation of blood. Vessels engorged. Thrombosis. Crumbling. Ovaries: Right, large follicle cyst. No corpus luteum. Left, Several persisting follicles. No corpus luteum. Myometrium: Some "chronic metritis."

CASE 15.—A. M. Path. No. 13310. Age forty-four. Married, 1 child. Metrorrhagia, 5 months, after delayed menses. Previous curetting. Endometrium: Gland dysplasia. Mixed phases. Swiss-cheese formation. Blood extravasation with engorgement and thrombosis of vessels. Ovaries: Right, several small follicular cysts. No corpus luteum. Left, follicular cyst. No corpus luteum. Myometrium: Enormous hypertrophy.

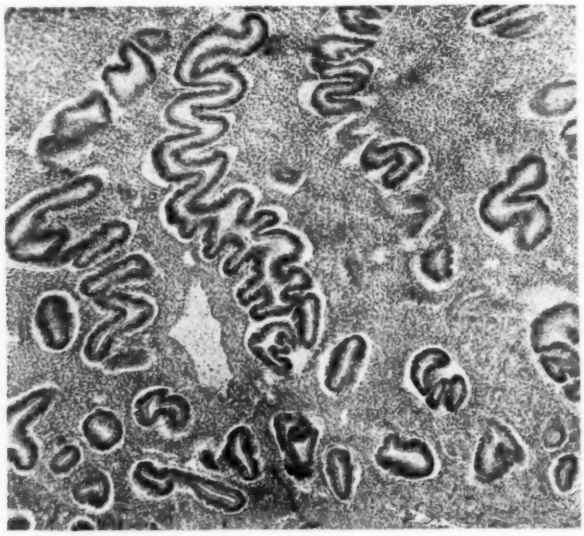

Fig. 5.—A close-up of a normal gland in the proliferative stage. It illustrates well the term "Schlängelung" (snakiness) used by the Germans.

CASE 16.—A. J. Path. No. 13640. Age thirty-seven. Married, 2 children. Menorrhagia with metrorrhagic spotting. Endometrium: Gland dysplasia. Mixed phases. Much dilatation. Areas of subepithelial extravasation of blood. Marked thrombosis of vessels. Ovaries: Right, several cystic follicles. No sign of corpus luteum. One persistent follicle with rich granulosa. Left, several follicle cysts. No corpus luteum. Myometrium: Moderate hypertrophy.

CASE 17.—E. S. Path. No. 13985. Age forty-seven. Single. Metrorrhagia, 3 months. One ovary removed at previous operation. Endometrium: Gland dysplasia. Enormous hypertrophy and hyperplasia. Bizarre. Swiss-cheese formation. Subepithelial extravasation of blood with local necroses. Ovary: (Single.) Two follicle cysts. No corpus luteum. Myometrium: Hypertrophied.

CASE 18.—M. K. Path. No. 17434. Age forty-eight. Married, no children. Metrorrhagia, 2 months. One ovary removed 12 years before. Endometrium: Gland dysplasia. Mixed phases in profusion. Swiss-cheese formation. Traces of

old blood in stroma. Desquamation of compacta. Adenomyosis in one cornu. Ovary: (Single.) Old follicle cyst, losing its lining. No corpus luteum. Myometrium: No hypertrophy.

HYSTERECTOMY SERIES: DYSFUNCTIONAL BLEEDING. 18 CASES

CLINICAL DATA

	Cases
Age:	
20-30	1
30-40	5
40-51	12
Condition:	
Married	15
Single	3
Pregnancies in 15 Married Women:	
Fertile	14
Sterile	1
Total number of pregnancies	57
Average	3.8
Symptomatology:	
Metrorrhagia	17
Menorrhagia (atypical)	1

MYOMETRIUM

	Cases
Hypertrophied	9
No change	7
"Metritis"	2

OVARIES

Corpus Luteum absent	10
Old degenerating corpora lutea	8
Recent corpora lutea	0
Follicle cysts present	18

ENDOMETRIUM

Gland dysplasia	18
Subepithelial hemorrhage with local necrosis	18
Previously curetted (within 6 months)	4

A perusal of the foregoing cases will show that the results of analysis tally closely with those of Schroeder. The chief points to be noted are:

1. Arhythmic metrorrhagia appeared in the histories of 17 of the 18 cases. One showed a severe polymenorrhea, with prolonged flowing.

2. In every case the endometrium revealed a characteristic dysplasia of the glands.

3. In 10 cases no corpus luteum could be found microscopically or macroscopically. In 8 cases there was evidence of old degenerating corpora lutea, antedating a normal cycle.

4. In all 18 cases, one or more cystic follicles were found in one or both ovaries.

5. In all 18 cases, subepithelial hemorrhage was present in the endometrium, and in many there were localized areas of vessel-thrombosis with necrosis and crumbling of the mucosa. This observation, strongly emphasized by Schroeder, has been frequently denied by others.

* * * * * *

II. The next investigation undertaken was a clinical and histological analysis of 237 consecutive private cases biopsied and treated with radium for excessive or untimely bleeding. The list comprises only cases in which the preoperative examination detected no associated pathology other than that of small fibroids. In this analysis numerous data of clinical interest were revealed, but these will be reserved for a later report. Interest for the present centers chiefly on the question of the frequency of gland dysplasia and the relationship of small fibroids in dysfunctional uterine bleeding.

The occurrence of gland dysplasia with dysfunctional bleeding has been variously estimated as from 10 per cent by Schickele and Keller up to approximately 100 per cent by Schroeder, Emil Novak, and

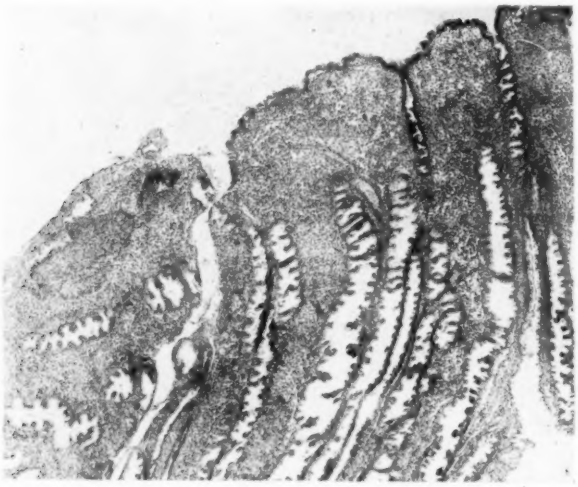

Fig. 6.—Typical premenstrual endometrium. The saw-toothed (sägefömig) character of the glands is well shown. Under higher power the epithelium would be seen to be tufted and beaker-shaped, with evidences of secretion in the gland lumens. If this picture is uniform throughout the endometrium, it may confidently be said that the corpus granulosum is normal and that the following menstruation will be on time and consistent in amount with the normal habit of the patient.

others. Adler denies any connection between glandular changes and abnormal bleeding. (Halban-Seitz, IV, Band, p. 150.)

In my first draft of the present series, the laboratory reports recorded 51 per cent of gland dysplasia. In order to test the accuracy of this finding, I reviewed the biopsy sections in the entire series and found the actual figure to be 81 per cent of dysplasia, many of the original diagnoses requiring correction. In this work I was assisted by Dr. George V. Smith, in order that the error of personal equation might be avoided.

An analysis was then made of the remaining 19 per cent (46 cases) in which gland dysplasia was absent. Six of these cases can be discarded on account of the presence of mucous or myomatous polyps which had probably provoked accidental and not dysfunctional bleed-

ing. In 16 cases the endometrium was atrophic or too fragmentary for accurate diagnosis, most of the patients having passed the menopause. Several had had previous irradiation. These cases can also be discounted as not being entirely pertinent. Of the 24 remaining cases that showed a normal interval endometrium, 22 were of the periodic-menorrhagia or prolonged-menopause type. This left two cases of normal endometrium in the presence of typical functional metrorrhagia. One of these had had a recent therapeutic curettage, the biopsy from which was not available. In the other the curettings, though normal, were too scanty for satisfactory diagnosis.

The foregoing evidence, taken in conjunction with that from the two series of hysterectomy cases here reported, strongly supports the

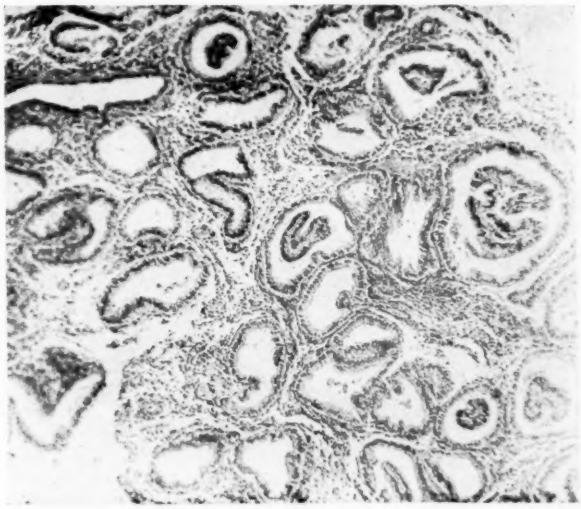

Fig. 7.—Gland dysplasia in the form of a general but uniform hypertrophy. The patient, thirty-two years of age, had periodic but profuse and prolonged menstruation. This appearance is sometimes mistaken for malignancy.

opinion that gland dysplasia is almost universally present in arhythmic dysfunctional bleeding, and that it may or may not be present in the periodic menorrhagias.

(In this connection it should be stated that metrorrhagia appeared in the entire series in the ratio of about 56 to 60 per cent, the exact figure being undetermined on account of faulty details in some of the histories.)

* * * * * *

III. The next subject of investigation was the relationship of fibroid tumors to dysfunctional bleeding. The preoperative examination notes of the 237 cases treated with radium revealed the presence of small fibroids in approximately 50 per cent of the entire number. Most of these tumors were evident; many were mentioned as suspected or probable. But careful study, both of the histories and of the endo-

metria, disclosed no clinical or histologic differences between the non-fibroid and the fibroid groups.

This observation supports the belief generally but not universally held that the abnormal bleeding associated with fibroids is identical in etiology and character with that of so-called idiopathic hemorrhage. The rule does not, however, apply to pedunculated fibroids, degenerating submucous fibroids and exposed uterine adenomyomata, conditions that require further study.

In order to gain additional information on the nature of the bleeding of fibroids, a study was next made of the uteri and ovaries of 25 patients subjected to hysterectomy and removal of the adnexa for large fibroid tumors. This group comprised cases with histories both

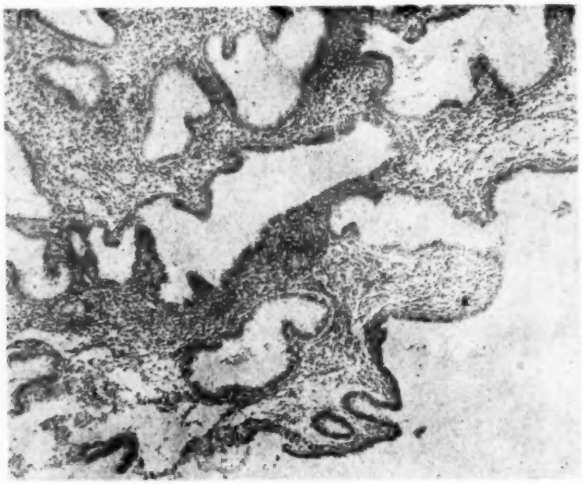

Fig. 8.—Gland dysplasia, showing moderate so-called dilatation of the glands. The picture is included in order to show that the widening of the glands is not a dilatation in the sense of an obstructive cystic retention, but rather, a true hypertrophy. No evidence of secretion can be seen, and in one place a dilated gland is shown with a distended, instead of a constricted or occluded, opening.

of normal and abnormal bleeding. It was hoped by this means to check up the histologic changes of the ovaries and endometrium associated with metrorrhagia with a parallel picture of what occurs during the normal menstrual cycle.

Abstracts of the several cases with the histories and histologic findings are given, together with a tabulation of the results.

LARGE FIBROID SERIES: DYSFUNCTIONAL BLEEDING

CASE 1.—J. C. Path. No. 17431. Age forty-four. Single. Menstruation: Regular, profuse. Last eta. 17 days. Endometrium: Normal early premenstrual stage. Ovaries: (One had been previously removed.) Fresh, young corpus luteum. Remains of old corpus luteum. Two follicle cysts. Myometrium: Large fibroids. Note: Normal physiology.

CASE 2.—E. H. Path. No. 17438. Age forty-four. Married, 2 children, 1 miscarriage. Menstruation: Regular, profuse. Last eta. 10 days. Endometrium:

Normal proliferative stage. Ovaries: Right, fresh corpus luteum. Old collapsed corpus luteum. Left, several follicle cysts. Myometrium: Multiple fibroids. Note: Normal physiology.

CASE 3.—E. L. Path. No. 17487. Age forty-one. Married, 3 children, 1 miscarriage. Menstruation: Normal. Last eta. 65 days. Pregnant. Endometrium: Decidua, early pregnancy. Ovaries: Right, corpus luteum of pregnancy. Left, no cystic follicles. Myometrium: Large fibroid. Note: Normal physiology. Pregnancy.

CASE 4.—A. H. Path. No. 17484. Age fifty. Married. Menstruation: Metrorrhagia, 2 months, continuous. Endometrium: Scattered areas of moderate dysplasia with superficial necrosis, adenomyosis. Ovaries: Right, no corpus luteum. No cystic follicles. Left, large dermoid cyst. No corpus luteum. Myometrium: Large fibroid with adenomyosis. Note: Normal physiology.

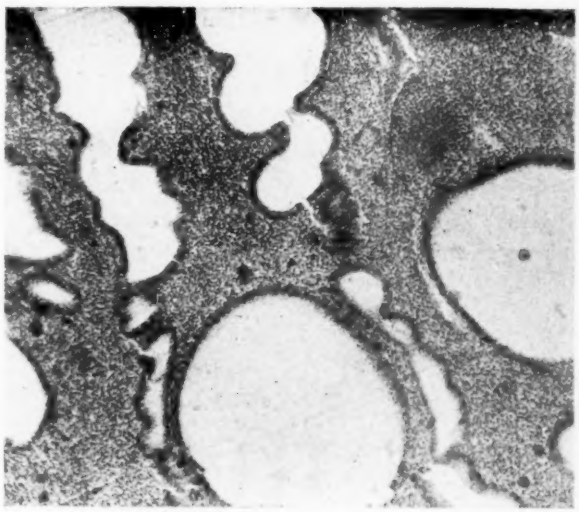

Fig. 9.—Gland dysplasia, showing wide dilatation of the glands in the form called by Novak the "swiss-cheese" type. This appearance is extremely characteristic and appears to a greater or less extent in most of the dysplastic endometria. The patient in this case was 43 years old and suffered from severe continuous metrorrhagia.

CASE 5.—J. C. Path. No. 17370. Age forty-eight. Married, 3 children, 1 miscarriage. Menstruation: 21- to 28-day cycle. Last eta. 15 days. Endometrium: Normal proliferative stage. Ovaries: Right, fragmentary; corpus luteum had been adherent and left in pelvis. Left, no corpus luteum. No cystic follicles. Myometrium: Multiple fibroids. Note: Normal physiology.

CASE 6.—M. L. Path. No. 14442. Age thirty-seven. Married, 5 children. Menstruation: Normal. Last eta. 11 days. Endometrium: Normal proliferative stage. Ovaries: Right, no corpus luteum. No cystic follicles. Left, fresh corpus luteum. One very small cystic follicle. Myometrium: Multiple fibroids. Note: Normal physiology.

CASE 7.—A. G. Path. No. 17057. Age forty-eight. Single. Menstruation: Menorrhagia, metrorrhagia. Skipping followed by constant metrorrhagia. Endometrium: Marked dysplasia. Adenomyosis showing the same type of glands. Ovaries: Right, small follicle cyst. No corpus luteum. Left, large follicle cyst. No corpus luteum. Myometrium: Large fibroids with adenomyosis. Note: Dysfunctional bleeding with typical histology.

CASE 8.—M. S. Path. No. 17457. Age thirty-three. Married, 1 child. Menstruation: Normal. Last eta. 20 days. Endometrium: Normal early premenstrual stage. Ovaries: Right, normal follicle atresia. Left, well-developed recent corpus luteum. Myometrium: Multiple fibroids. Note: Normal physiology.

CASE 9.—M. B. Path. No. 17117. Age forty-seven. Married. Menstruation: Menopause 14 months. Constant staining 2 months. Endometrium: Atrophy and dysplasia, with endometritis. Ovaries: Right, follicle cyst. Left, small serous cystoma. Myometrium: Large fibroid. Note: Postclimacteric dysfunctional bleeding, with characteristic changes.

CASE 10.—A. P. Path. No. 17141. Age forty-seven. Married. Menstruation: Normal. Last eta. 8 days. Endometrium: Normal early proliferating stage. Ovaries: Right, normal involuting corpus luteum (1½ cm.). 1 follicle cyst. Left, cystic follicle. Myometrium: Multiple fibroids. Note: Normal physiology.

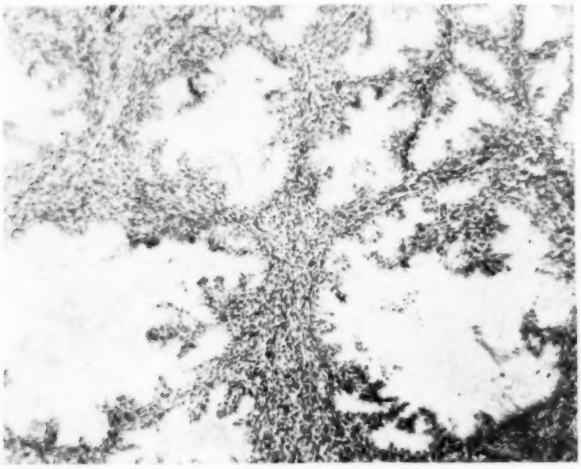

Fig. 10.—Gland dysplasia in a premenstrual endometrium. The glands are uniformly of the secretory type but show marked hypertrophy, evidently under the influence of, but not dominated by, a growth hormone. As would be expected from the picture, the patient (forty-five years of age) suffered from periodic menorrhagia. One would expect to find in the ovaries rhythmic but defective ovulation.

CASE 11.—R. W. Path. No. 17165. Age thirty-eight. Married, 3 children. Menstruation: Irregularly periodic: Menorrhagia. Last eta. 24 days. Endometrium: Premenstrual, mixed with proliferative, Swiss-cheese dysplasia. Ovaries: Right, several cystic follicles. One mature follicle with egg. Left, recent corpus luteum with thinned and flattened granulosa. Somewhat cystic. Myometrium: Large fibroid. Note: This case illustrates the effect of a defective corpus luteum, not sufficiently strong to counteract the follicle action.

CASE 12.—E. G. Path. No. 17173. Age thirty. Single. Menstruation: Periodic, profuse. Last eta. 21 days. Endometrium: Normal early premenstrual stage. Ovaries: Right, corpus luteum. Granulosa somewhat flattened. Several small cystic follicles. Left, numerous small cystic follicles. Myometrium: Large fibroid. Note: Slight deviation from normal.

CASE 13.—M. G. Path. No. 17203. Age forty-five. Married, 1 child. Menstruation: Metrorrhagia, constant for 1 year. Endometrium: Marked gland dysplasia. Proliferative. Swiss-cheese type. Ovaries: (One ovary removed 3 years before.) Large follicle cyst. No corpus luteum. Myometrium: Large fibroid. Note: Dysfunctional bleeding with typical histology.

CASE 14.—G. C. Path. No. 17229. Age forty-four. Married, 4 children. Menstruation: Normal. Last eta. 21 days. Endometrium: Normal premenstrual stage. Ovaries: Right, normal corpus luteum, a few atretic follicles. Left, a few atretic follicles. Myometrium: Multiple fibroids. Note: Normal physiology.

CASE 15.—E. C. Path. No. 17440. Age thirty-eight. Married. Menstruation: Normal. Last eta. 18 days. Endometrium: Normal proliferative stage. Ovaries: Right, matured corpus luteum ,beginning fibrosis. Left, numerous active immature follicles. Some follicle atresia. One follicle evidently just after rupture. Myometrium: Multiple fibroid. Adenomyosis in one cornu. Note: Normal physiology just after ovulation.

CASE 16.—A. M. Path. No. 17239. Age forty-three. Married. Menstruation: Menorrhagia, 6 years. Metrorrhagia, 2 months. Endometrium: Typical gland dysplasia. Ovaries: Right, small. No cysts. No corpus luteum. Left, two large follicle cysts. No corpus luteum. Myometrium: Large fibroid. Note: Dysfunctional bleeding with typical histology.

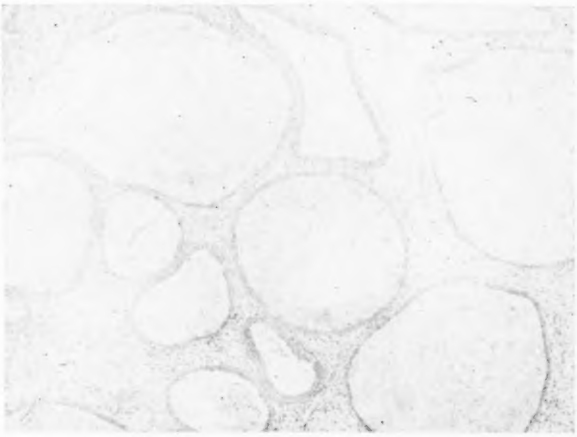

Fig. 11.—Dysplasia, postclimacteric. Endometrium from a patient of sixty-six years with nonmalignant bleeding. There was also an endometrial polyp present. The etiology in cases of this kind is problematic.

CASE 17.—L. E. Path. No. 17255. Age forty-seven. Married. Menstruation: Normal. Last eta. 19 days. Endometrium: Late proliferative stage, with slight dilatation. Ovaries: Right, no follicle cysts. Left, fresh corpus luteum. No follicle cysts. Myometrium: Leiomyosarcoma. Tubercular salpingitis. Note: Normal physiology in the presence of serious pelvic disease.

CASE 18.—B. F. Path. No. 17261. Age forty. Married. Menstruation: Normal. Last eta. 16 days. Endometrium: Normal proliferative stage. Ovaries: Right, no cysts. Left, fresh corpus luteum. No cysts. Myometrium: Large fibroid. Note: Normal physiology.

CASE 19.—J. W. Path. No. 17405. Age forty-five. Married, 1 child. Menstruation: Polymenorrhea, rhythmic, with severe menorrhagia. Last eta. 14 days. Endometrium: Premenstrual stage (note frequent periods). Ovaries: Right, follicle cyst. Left, corpus luteum cyst. Lutein cells disintegrating. Myometrium: Multiple fibroids, with adenomyosis. Note: Deviation from normal, with picture somewhat confused.

CASE 20.—A. G. Path. No. 17390. Age thirty-nine. Married, 1 child. Menstruation: Normal. Last eta. 27 days. Endometrium: Normal premenstrual stage. Ovaries: Right, ripe corpus luteum. No follicle cysts. Left, early maturing

graafian follicle. No cysts. Myometrium: Multiple fibroids. Note: Study this for perfect timing of endometrium, corpus luteum and young follicle.

CASE 21.—R. C. Path. No. 17035. Age forty-six. Married, 6 children, 2 miscarriages. Menstruation: Normal. Last eta. 21 days. Endometrium: Prolifera-

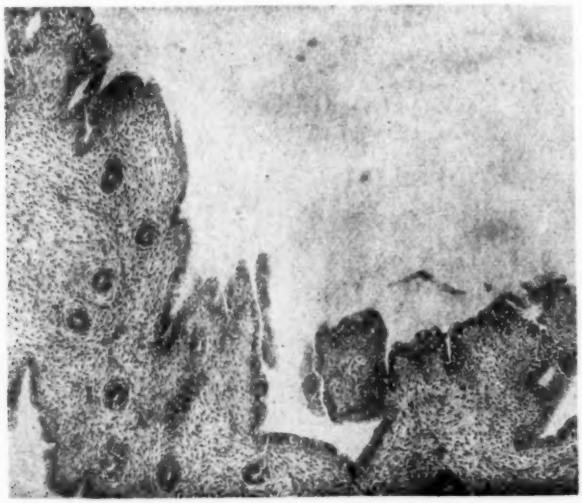

Fig. 12.—Gland dysplasia of mixed type. The picture shows marked polypoid hypertrophy of the stroma in which are seen glands in the rest stage. Other curettings from this same case showed swiss-cheese hyperplasia of the glands with little stroma. The patient, forty-eight years old, was treated for metrorrhagia.

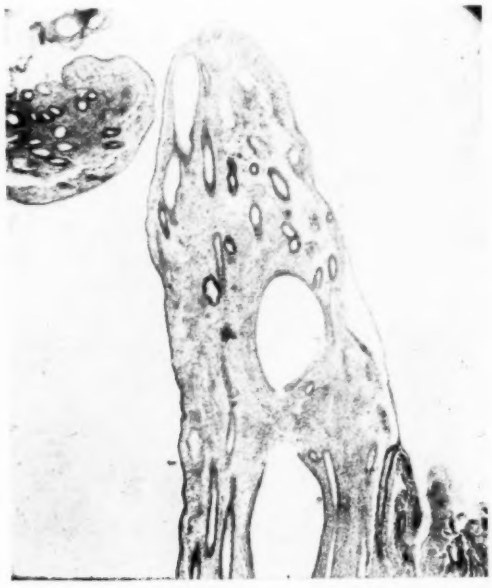

Fig. 13.—Gland dysplasia in a girl of 24 years, with long-standing continuous metrorrhagia. The polypoid hypertrophy of the endometrium and "swiss-cheese" gland hyperplasia side by side with glands in the rest stage are depicted.

tive stage, with very early premenstrual changes. Ovaries: Right, normal follicle atresia. Left, fresh corpus luteum. No cysts. Myometrium: Large fibroid. Note: Normal physiology.

CASE 22.—C. C. Path. No. 17115. Age forty-eight. Single. Menstruation: Metrorrhagia, 2 years. (Record incomplete.) Endometrium: Atrophied. Ovaries: Right, numerous cystic follicles. No corpus luteum. Left, numerous cystic and hemorrhagic follicles. No corpus luteum. Myometrium: Large fibroid. Note: Probably case of postclimacteric dysfunctional bleeding. Gland dysplasia absent.

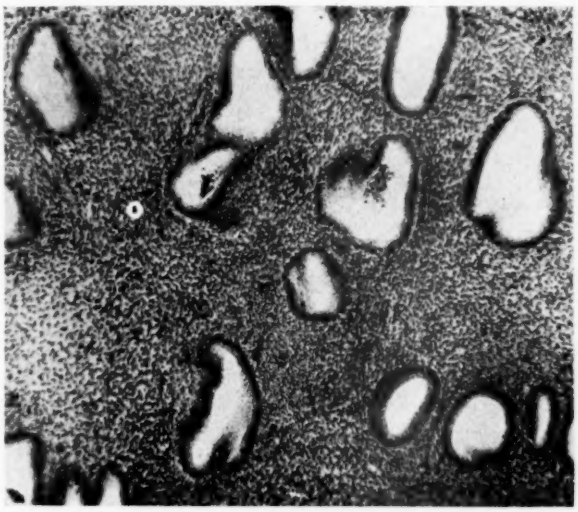

Fig. 14-A.—Gland dysplasia, mixed type. This picture shows a moderately hypertrophied endometrium of the proliferative stage. Its significance lies in its association with premenstrual changes seen in other sections (Fig. 14-B). The patient, forty years old, suffered from severe periodic menorrhagia.

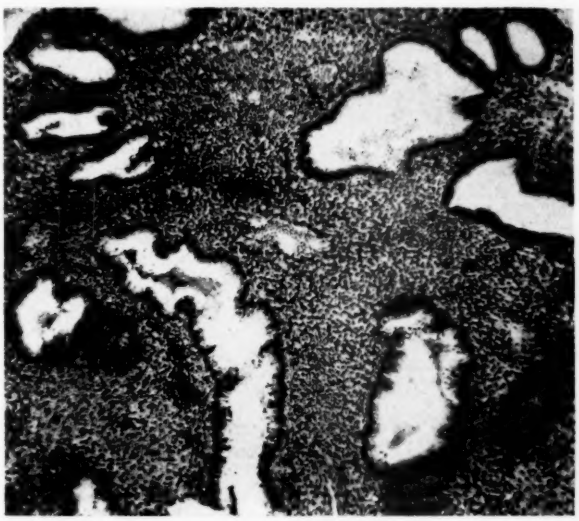

Fig. 14-B.—Same as Fig. 14-A. Hypertrophied proliferative glands side by side with glands that show atypical premenstrual changes.

CASE 23.—C. L. Path. No. 17024. Age forty-seven. Married, 2 children. Menstruation: Metrorrhagia and skipping for 3 months. Endometrium: Typical gland dysplasia. Ovaries: Right, old disintegrating corpus luteum cyst. Left, no corpus luteum. No cystic follicles. Myometrium: Multiple fibroids. Note: Dysfunctional bleeding with typical histologic changes.

CASE 24.—B. B. Path. No. 17296. Age thirty-seven. Married, 1 child. Menstruation: Two periods previous month. Last eta. 30 days. Endometrium: Moderate dysplasia. Ovaries: Right, old degenerating corpus luteum. Large retention cyst. Left, several cystic follicles. Myometrium: Large fibroid. Note: Deviation from normal. Recent menstrual irregularity.

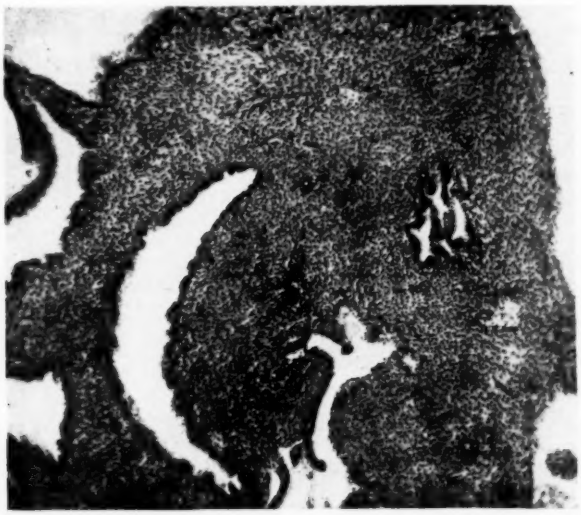

Fig. 15-A.—Gland dysplasia, mixed type, showing marked hypertrophy of the stroma associated with dilatation of the glands. Patient fifty years old, with severe metrorrhagia for eight weeks.

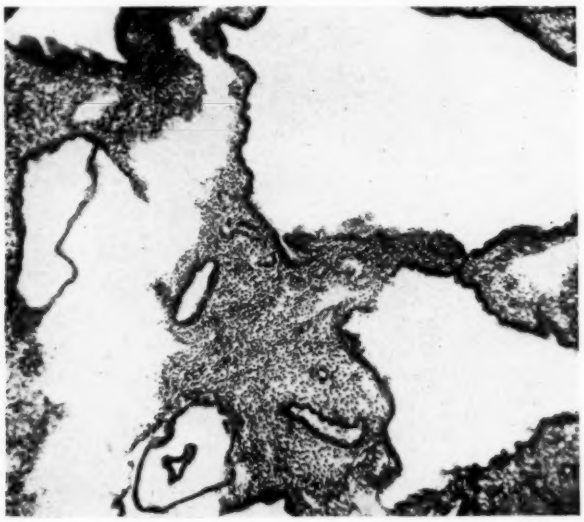

Fig. 15-B.—Same case as preceding figure. Mixed gland dysplasia, showing great irregularity and dilatation of glands. Slight evidences of secretory changes.

CASE 25.—R. H. Path. No. 17522. Age fifty-one. Married, 1 child. Menstruation: Normal, but last eta. 33 days. Endometrium: Partly normal premenstrual, partly proliferative, with slight dysplasia. Ovaries: Right, negative. Left, ripe corpus luteum. Granulosa cells infiltrated with blood. Myometrium: Multiple fibroids.

From a perusal of the foregoing abstracts it will be seen that of the 25 cases 14 had a history of normal menstruation, and in each of these was found an endometrium corresponding in its phase to the development of the corpus luteum, which was always consistent in age with the date of the preceding menstruation. The time of ovulation, however, varied, though in no case was it delayed beyond the seventeenth day. In one instance it had taken place by the eighth day, and in one by the eleventh day. This variation has been noted by others. One case, complicated by an early pregnancy, was included to emphasize still further that the ovaries and endometrium may functionate normally even in the presence of large fibroids.

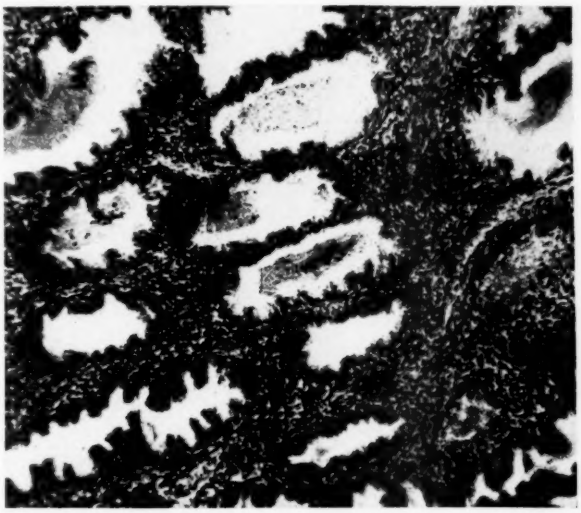

Fig. 15-C.—Same case as two preceding figures, showing portion of endometrium with typical secretory or premenstrual changes in the glands. These three phases of the same endometrium illustrate the imbalance that exists between the two ovarian hormones when a corpus luteum is present but defective.

Besides the normally functioning cases, 4 with polymenorrhea and 7 with typical metrorrhagia were included. In all these 11 cases, gland dysplasia and aberrations in the development of the corpus luteum appeared, reproducing exactly the picture seen in the series of 18 cases first described, in which no fibroids were present.

The results of these studies lead to the conclusion that the bleeding of fibroid tumors (with the exceptions noted) is purely functional and in no way specific.

* * * * * *

IV. An important factor in the problem of dysfunctional bleeding is the rôle played by the cystic follicles. In the typically metrorrhagic (i.e., arhythmic) cases of the first and third groups, follicle cysts were always present. In the seminormal (polymenorrheic) cases they appeared in conjunction with defective corpora lutea. In the function-

LARGE FIBROID SERIES TABULATED

CASE	AGE	COND.	PREG.	MENSTR.	LAST CTA.	OVARIES		ENDOMETRIUM
						CORPUS LUTEUM	FOLL. CYSTS	
1	44	S	0	Normal	17 days	Normal	Two	Early premenstrual
2	44	M	3	Normal	10 days	Normal	Several	Proliferative
3	41	M	4	Normal	65 days	Normal	None	Decidua of preg.
4	50	M	0	Metrorrh.	2 mo. flow	Absent	Dermoid	Dysplasia
5	48	M	4	Irreg.	15 days	Normal	None	Proliferative
6	37	M	5	Normal	11 days	Normal	1 small	Proliferative
7	48	S	0	Metrorrh.	Constant	Absent	1 large	Dysplasia
8	33	M	1	Normal	20 days	Normal	None	Premenstrual
9	47	M	0	Metrorrh.	14 mo.	Absent	Two	Dysplasia-atrophy
10	47	M	0	Normal	8 days	Normal	Two	Proliferative
11	38	M	3	Irreg.	24 days	Defective	Several	Premenstr. & prolif.
12	30	S	0	Normal	21 days	Normal	Several	Premenstrual
13	45	M	1	Metrorrh.	Constant	Absent	1 large	Dysplasia
14	44	M	4	Normal	21 days	Normal	None	Premenstrual
15	38	M	0	Normal	18 days	Normal	None	Proliferative
16	43	M	0	Metrorrh.	Constant	Absent	2 large	Dysplasia
17	47	M	0	Normal	19 days	Normal	None	Proliferative
18	40	M	0	Normal	16 days	Normal	None	Proliferative
19	45	M	1	Polymen.	14 days	Cystic	One	Premenstrual
20	39	M	1	Normal	28 days	Normal	None	Premenstrual
21	46	M	8	Normal	21 days	Normal	None	Premenstrual
22	48	S	0	Metrorrh.	Constant	Absent	Numerous	Atrophied
23	47	M	2	Metrorrh.	3 mo.	Cystic	None	Dysplasia
24	37	M	1	1 irreg.	30 days	Over-ripe	1 large	Dysplasia—mild
25	51	M	1	Delayed	33 days	Over-ripe	None	Dysplasia—slight

ally normal cases they were often insignificant, often absent. According to Schroeder's creed, dysplasia of the endometrium with its consequent bleeding is produced by the accumulation of growth-hormone in the persisting follicles. Recent discoveries tend to modify this doctrine.

The younger persistent follicles in my series showed a rich granulosa lining, which was undoubtedly active. But the epithelium of the older follicle cysts in the long-standing cases appeared meager and was often absent entirely, so that the cysts gave the impression of inert organs.

In four cases where it was possible to secure fresh sterile material, the liquor from these older cysts was injected into spayed rats to determine its hormone potency, but each time without reaction. These experiments are too few in number for definite conclusions. They merely lend weight to a growing belief that the follicle cytosis, gland dysplasia and failure of the corpus luteum are all incidental phenomena resulting from or intensified by the disturbance of some more powerful hormone higher up in the endocrine scale. Suggestive, also, are the cases of gland dysplasia, follicle cytosis and bleeding that occur in patients after the menopause, where a motor impulse from the germ plasm is out of the question.

* * * * * *

V. A study of the uterine blood in functional metrorrhagia was initiated by making a daily examination of the discharges from a girl of twenty-three with long-standing idiopathic hemorrhage. Later biopsy from curettage revealed a marked gland dysplasia. Microscopic examination of the uterine blood failed to show the characteristic endometrial remnants seen in normal menstruation. This single observation taken in conjunction with the nearly universal occurrence of clotting in our cases supports the conclusion, otherwise logical, that the blood of dysfunctional hemorrhage is deficient in, or entirely lacks, the secretory elements that would be induced by a normal corpus luteum. In other words, it approaches, or may be equivalent to, an ordinary body hemorrhage, according to the extent of the functional disturbance. This probably explains the severe and uncontrollable hemorrhages that are frequently encountered.

* * * * * *

VI. The theory of the etiology of dysfunctional uterine hemorrhages advocated in this paper assumes a twofold hormone of the ovary. At the present day this assumption hardly needs confirmation. Dr. Smith of the Free Hospital for Women, working with Corner's lipoid extract of corpus luteum, has entirely substantiated Dr. Corner's well-known results. He has also discovered new evidence of the specificity of the corpus luteum hormone by demonstrating distinctive reactions in the blood chemistry of experimental animals under conditions of

ovulation, pregnancy and castration. This constitutes a new and apparently rich field of research. Dr. Smith will publish his observations in a later monograph.

SUMMARY

1. Metrorrhagia (arhythmic dysfunctional uterine bleeding) is associated with complete absence or marked defectiveness of the corpus luteum.

2. The bleeding of metrorrhagia is the result of localized necroses in a dysplastic endometrium.

3. Typical dysfunctional metrorrhagia is almost constantly associated with endometrial dysplasia.

4. Endometrial dysplasia is produced by the abnormal continuation of the unantagonized follicle hormone and is constantly associated with follicle cystosis. A possible influence from the anterior pituitary must be considered.

5. In *periodic* dysfunctional bleeding both the follicle and corpus luteum hormones are present, but in a state of physiologic imbalance. Gland dysplasia may or may not be present according to the extent of the disturbance.

6. The bleeding of fibroid tumors (with exceptions noted) is dysfunctional in nature and is morphologically and physiologically identical with that from nonfibroid uteri.

7. The specificity of the corpus luteum hormone in contrast to that of the follicle has been confirmed by Smith, first by a repetition of Corner's work, and secondly by the discovery of distinctive reactions in the blood chemistry of experimental animals under various sexual conditions.

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198 COMMONWEALTH AVE.

THE QUESTION OF POSSIBLE ENDOMETRIAL TRAUMA AND DISLOCATION ASSOCIATING UTEROTUBAL INSUFFLATION

By I. C. Rubin, M.D., F.A.C.S., New York City

THE possibility of dislocating endometrial particles as a result of uterotubal insufflation must have occurred to many since Sampson's epochal reports on the pathology and etiology of endometriomata.[1] Although I have not encountered a single instance in which tubal insufflation caused peritoneal endometriomata it is well to inquire into the possibilities and probabilities. Sampson makes no mention of tubal insufflation in connection with his reported cases of endometriomata. Search of the recent medical literature shows that others have mentioned the etiologic relationship between them without, however, adducing evidence to support their hypothesis. It is the major purpose of this paper to discuss this question.

Two serious dangers engaged my attention at the onset. The first was that of introducing infection along with the gas into the peritoneal cavity via the tubes and the second was gas embolism. These have been dealt with in a number of publications. The contraindications to the performance of uterotubal insufflation have been repeatedly stated. They cannot be overemphasized. Briefly they are as follows: (1) the presence of infective secretions caused by Bartholinitis, urethritis, vaginitis, cervicitis; (2) bleeding from the genital tract; (3) inflammatory pelvic masses; (4) pelvic tenderness without palpable masses; (5) physiologic or pathologic pregnancy or suspicion of pregnancy. Scrupulous attention to these contraindications which were at first based upon general gynecologic experience and principles was considered sufficient to eliminate the danger of infection in practically all cases. Careful regard for points in technic further reduce possible bad results to a negligible minimum.

The significant record of 3000 cases examined by this method at the Woman's Hospital without a serious mishap as reported by George G. Ward points to its safety.[2] Similar results have been reported from Mt. Sinai Hospital and other American hospitals, too well known and numerous to mention in this brief communication, where this method has been properly employed.*

The effect of gas entering the venous circulation, an accident which might well be caused by traumatizing the uterine mucosa with the cannula, had already been estimated by an early experiment. Oxygen was introduced directly into the saphenous vein of a dog at a rate

*For some of the more important references see Rubin, Am. Jour. Obst. & Gynec. 17, No. 4, 484, April, 1929; also Anspach, Brooke, M., Am. Jour. Obst. and Gynec.

flow which was employed in uterotubal insufflation. The amount of gas used was in excess of the quantity needed for clinical purposes. The animal tolerated the gas in the blood stream very well as the gas bubbles percolated into the vein under a minimum pressure, demonstrating that small bubbles are evidently taken up by the blood where they are distributed and absorbed by the erythrocytes without causing cardiac embarrassment. This single experiment added to the experience with intravenous oxygen therapy obtained during the late war, justified the conclusion that a small quantity of oxygen may be supported by the blood stream and that when administered slowly it does not give rise to embolism whether this be introduced into a peripheral vein or into the parenchymatous veins of an organ such as the uterus.

When however gas is forced under great pressure into the uterine veins through a traumatized endometrium, acute cardiac dilatation and collapse may result. This has actually happened resulting in death in a case which has come to my notice and which I have reported after investigating the circumstances.* The cervix and uterine mucosa in this case were first traumatized by cervical dilatation and curettage. This operation was then followed by uterotubal insufflation under high pressure. The patient had previously had an amputation of the cervix and at the time the uterus was insufflated there were present multiple fibroids and bilateral pyosalpinx. The avenues of entry being laid widely bare, the gas entered the venous circulation forcibly and in large quantity. The patient did not recover from the anesthesia. At the postmortem, large collections of oxygen were found in the iliac veins and inferior vena cava, as well as in the right heart. It is extremely doubtful if this tragic outcome would have occurred unless the oxygen was retained within the uterine cavity and the tubes in large volume. In that instance the curettage must have immediately followed the insufflation. The reverse order, i.e., curettage followed by the insufflation as testified to by the assistants present, would more logically explain the death.

This tragic experience has served to illustrate the extreme effects of forcible injection of gas in the presence of ruptured blood vessels.

In my early experiments upon extirpated uteri I was struck by the fact that the gas in a few instances escaped through the uterine veins. Upon examining the specimens carefully it was noted that the mucosa had been seriously injured during hysterectomy and that the uterus was roughly handled and squeezed. When care was exercised in the removal of the uterus, the uterine mucosa being left intact, leakage

*Case later mentioned by Moench in the J. A. M. A., Aug. 13, 1927. My investigation of this case resulted in different findings. The doctor who performed the operation had stated that he dilated and curetted after insufflating the uterus. It will only suffice to point out this error in judgment by calling attention to the fact that when the insufflation demonstrated closed tubes he proceeded nevertheless to do a curettage. The spectators present at the operation asserted that the curettage preceded the insufflation which is more likely, because had the curettage followed the insufflation by a few minutes no such calamity would have occurred.

through the vessels did not occur when gas was insufflated into the extirpated uterus. This gross trauma is of course not to be considered in the clinical performance of uterotubal insufflation.

Sampson has shown that during menstruation it is possible to force opaque material such as barium sulphate or bismuth in suspension into the "receiving" venous sinuses. *In the nonmenstruating state this cannot be done as the intact endometrium protects the veins.* The latter are naturally laid open during the menstrual desiccation. Sampson's radiographic pictures demonstrate the difference between menstruating and nonmenstruating mucosae.[3] The trauma of curettage increases the injury to the uterine venous sinuses to a marked degree. *Uterine insufflation should never be done after a curettage or in the presence of uterine bleeding.*

In one of my early cases an attack of syncope occurring as soon as the patient rose from the examining table may have been due to trauma to the mucosa and the blood vessels of the cervix. The uterine cannula used in that case had been hammered out of shape by the nurse when she attempted to clean it out before the insufflation. Apparently the mucous lining of the stenosed cervical canal in that case was traumatized and the gas probably entered the blood vessels under a pressure of 200 mm. Hg. The patient regained consciousness within three minutes and suffered no other consequence. This avoidable accident, however, serves to illustrate the effect of trauma, and indicates the necessity of gentleness in employing the test. A smooth, highly polished cannula is essential. Fainting is not an utterly rare occurrence in office practice and need not be associated with vessel trauma. But the possibility of a circulatory disturbance as a cause of syncope must be borne in mind. A genuine attack of epilepsy was evidently precipitated by an insufflation in one of my cases. No unusual features were noted during the examination. Nor was my attention called to her convulsive tendency in the history. Upon inquiry she said that she had fallen faint on the street and elsewhere. Her husband added information which left no question as to the epileptic nature of her seizure.

Attention has been called to the postmenstrual phase; i.e., the fourth to the seventh day after cessation of the period as the most desirable and most favorable time to do the insufflation.[4] The mucosa is then regenerated; it is not yet swollen or succulent; it is relatively flat and the amount of mucosal secretion is minimal. The introduction of the cannula is not likely to be attended by injury to the mucosa in the postmenstrual phase because the spongy layer of the endometrium has not yet been fully developed. Furthermore, the gas is not likely to displace secretions from the uterine cavity into the tubes. This is in accord with Sampson's findings "that although the endometrium of the early part of the interval stage of the menstrual cycle is thin, it

offers complete protection against escape of material from the uterine cavity. Curet and this protection is removed exposing the sinuses."

Insufflation should be deferred when bleeding immediately follows an attempt to introduce a sound or cannula into the uterine cavity. In case a cervical stenosis is encountered it is necessary first to overcome the obstruction by dilatation. The insufflation can be left for a more suitable time. The indication for the performance of uterotubal insufflation is never so urgent as to warrant undue and unnecessary hazards. Since its purpose is to determine the presence or absence of tubal patency in a case of sterility of several years' standing, postponing the test for another month or two cannot be of vital importance.

The finding of fragments of endometrium within the tube lumen has been regarded as strong evidence in favor of the mechanical transportation of these particles in retrograde fashion via the tubes from their source of origin to the peritoneal cavity where they may be deposited, become implanted, and develop into chocolate cysts.

In his later papers Sampson speaks of finding bits of endometrial tissue in the lumen of some of the tubes from whose fimbriated end *menstrual blood* was found to escape.[5] This was observed in patients operated upon during menstruation. Microscopic particles of uterine mucosa have been demonstrated within the fallopian tubes during the menstrual interval by a few observers. H. O. Neumann[6] has more recently reported upon three cases in which endometrium was demonstrable within the tube lumen. The fragments in two cases measured 1.5 : 1.0 : 0.6 mm. and 2.1 : 1.2 : 0.7 mm. These were not associated with endometriomata of the ovaries or of the peritoneal cavity. In the third cases masses of endometrial tissue were so voluminous lining the tube lumen as to resemble uterine mucosa. Sampson cysts were present on the same side. This author leaves open the question whether the fragments were freshly dislocated bits of uterine mucosa or whether they may have arisen through a heteroplasia of tubal epithelium. In none of these cases was mention made of tubal insufflation having preceded the operative removal of the tubes. Nevertheless on the basis of these three cases, among other conclusions, he ventures one that "the indications for tubal insufflation be restricted to a minimum and that hysterosalpingography be discarded altogether."[6]

Heim[7] reported finding an endometrial fragment 1.4 : 0.6 mm. in the midportion of a fallopian tube which he explained as caused by the uterine clamp squeezing the delicate mucosa and breaking off pieces which were pressed through the uterine ostia into the tubes. Neumann in accepting this explanation remarks that under persistent pressure of the uterine clamp the uterine muscle relaxes and consequently the intramural portion of the tube becomes wider. After investigating a larger number of extirpated tubes he has found that viable endometrial particles are not uncommon in the tubes. "All it requires is careful serial section of the tubes." He further warns against squeezing the uterus in conservative operations and points out that endometrial dislocation can result when the patient is examined several times under narcosis.

There can be no doubt that it should be possible experimentally to dislocate detached endometrial particles from the uterine cavity into the tubal lumen. Theoretically it should also be possible to displace

by uterotubal insufflation particles of desiccated menstrual mucosa through the tubes into the peritoneal cavity. I have felt that retrograde transportation through the tubes can take place during a curettage.[8] When vigorous uterine colic takes place the curette or irrigating uterine cannula can act as a stopper in the cervical canal. Irrigation might force these particles through the uterine ostiae of the tubes if care is not taken to withdraw the irrigator sufficiently often to allow for free escape of the irrigating fluid through the cervix. Kosmak[9] has shown that this can occur and I have reported a similar observation.[10] It would be of interest to note in how many cases of endometriosis one or more curettages may have been done previous to the operative findings of ectopic endometrial tissue and further whether irrigation had been used during the curettage. The use of irrigation has been abandoned by most gynecologists in the past decade. The operation of curettage, however, is often done by the general practitioner.

Experimental proof of the correctness of these claims might be obtained through systematic examinations of tubes removed at operation. The following plan for such a study suggests itself: 1. The uterus should be handled so as to avoid possible injury of the endometrium. If for technical reasons it must be grasped by uterine clamps or bullet forceps the tubes should first be clamped off at the interstitial portion. A control series of (a) curettements preliminary to the hysterectomy; (b) insufflation preliminary to the hysterectomy could be compared when, (1) the ordinary technic of hysterectomy is employed, and (2) when the tubes are clamped off first at their uterine junction before the uterus is grasped by any instrument; (3) clamping of only one tube in this way would still further control escape of endometrium into the unclamped tube. The amount of laboratory work entailed in such a task is obviously enormous, but when carried out would finally settle the question of mechanical dislodgment of endometrial particles.

I am in accord with Sampson in the theory that under certain conditions during menses endometrial particles can escape into the tubes. A well-marked cervical stenosis with hyperanteflexion can well form the predisposing basis of such an occurrence. That retrograde peristalsis takes place in the tubes was demonstrated by Wislocki and Guttmacher[11] and I have been able to confirm their observations both in animal experiments and with Bendick by clinical fluoroscopic examinations using lipiodol as the radio-opaque substance.[12, 13] The escape of blood from the fimbriated end of the tubes as observed by Sampson during menstruation is strongly suggestive of a back flow. The theory of independent tubal menstruation still remains a debated point. If the latter were true it would incidentally explain epithelial dislocation toward the peritoneum.

Whether or not the desquamated menstruating endometrial particles can take root in the serosa of the genitals or peritoneal lining of the pelvis is still open to question. Sampson believes that "endometrial tissue disseminated by menstruation is sometimes alive and will continue to grow, if transferred to situations suited to its growth."[13] He is convinced that the back flow of menstrual blood from the uterine cavity through the tubes is at least one of the important sources of the epithelium which results in peritoneal endometriosis. Jacobson[14] succeeded in producing peritoneal endometriosis by implanting small pieces of endometrial tissue (not of the menstrual phase) into rabbits and monkeys. Heim,[7] Caffier,[15] and Katz and Szenes[16] have moreover shown that such bits of viable endometrium may continue to grow in plasma culture in vitro. (The endometrial particles removed with the uterine cannula tip, presently to be described, may be utilized in the future for implantation and explantation experiments.) That epithelial débris contained in the menstrual blood is also capable of producing endometriomata still awaits experimental proof.

For endometrial dislocation to take place as a result of uterotubal insufflation one must assume the demonstrable presence of two conditions. 1. The uterine mucosa must be friable enough to be broken up into small particles by the cannula. 2. These particles must be demonstrated to be blown by the gas through the uterine ostia of the tubes. During observations made with the hysteroscope, using CO_2 for the insufflation, no such conditions were found.[10] The instrument used for this purpose requires no preliminary dilatation of the cervix.* The endometrium of the postmenstrual phase is not fragile or friable. Particles of mucosa were not seen to float loosely in the uterine cavity. It is purely a matter of speculation whether a chance bit of endometrium that might be broken loose by the uterine cannula might be of the exact size and carried in the right direction toward the tubes to actually make its way into them.

When the tip of the uterine cannula is examined after its withdrawal from the uterus it shows that in a certain number of cases a very small particle or several tiny particles of uterine mucosa are removed at the same time. These minute particles are found in the lumen of the tip of the cannula and in the small fenestra into which they have apparently been pressed. They may be removed from the cannula tip by attaching a rubber bulb to its distal end and washing through it. Simply blowing air through the cannula will not remove the particles as they adhere tenaciously to the metal. Several attempts may be found necessary to finally clean the cannula of the mucus and mucosal particles. This maneuver in itself demonstrates

*Mikulicz-Radecki in a personal communication states that with the use of his hysteroscope which requires preliminary dilatation and water irrigation, fragments of mucosa are torn off in an appreciable number of cases.

the unlikelihood of the gas displacing these particles from the cannula into the uterine cavity during uterotubal insufflation.

STUDY OF THE BITS OF MUCOSA REMOVED WITH THE UTERINE CANNULA

For purposes of study the particles are first dislodged into cold water. Formalin is then added to the desired strength. Microscopic study of these minute particles which, blocked en masse and making at most a very small specimen for microscopic section has nevertheless enabled us to get some idea of the amount of trauma to the endometrium incidental to uterotubal insufflation. The material obtained in this way has also been studied in connection with the question of the morphological relationship between the ovarian and endometrial cycle.

The particles of mucosa were examined from 90 cases. In 43 instances no tissue was obtained for laboratory purposes. In 47 instances one or several tiny fragments have been available for microscopic study. Of the 90 cases of sterility in which tubal insufflation was done 65 cases were of women who menstruated normally and 25 were of women who had varying periods of delayed menstruation. The amount of tissue from the amenorrhea cases was more apt to be scantier than from those with regular menstruation.

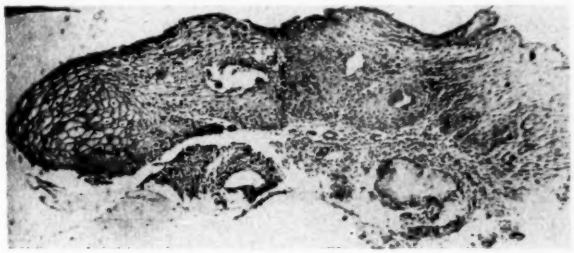

Fig. 1.—A tiny fragment of squamous epithelium with a cervix gland.

SUMMARY OF THE FINDINGS OF THE TYPE GLAND, CERVIX OR CORPUS

In 5 cases there were fragments of squamous epithelium and a few cervix glands or fragments of cervix glands (Fig. 1).

In 8 cases there were cervical glands or fragments of cervix glands with mucus detritus and small bits of stroma (Figs. 2 and 3).

Sixteen specimens showed cervix glands and endometrial glands or fragments of endometrial glands (Figs. 2 and 3). Seventeen specimens showed small numbers of endometrial glands with mucus detritus (Fig. 4). In one specimen only a small collection of stroma cells were seen and no glands (Fig. 5).

The following experiments have also yielded data bearing on the question of possible endometrial dislocation during uterotubal insufflation:

1. Before removing the cannula at the end of clinical insufflation the gas valve is shut. The rubber tubing near its connection with the cannula is squeezed between the fingers so as to maintain the same pressure within the tubing which was reached during the insufflation. The cannula is then inserted into a water bottle and the pressure of the fingers is released. It is carefully noted whether mucus or mucosal particles are thus expelled into the solution. Ejection of the particles by this

maneuver has not been observed. At most there is partial displacement from the lumen of the cannula but the particles are not completely extruded.

2. Another way of observing whether the particles are displaced by the streaming gas is to release the pressure within the cannula and reducing it to zero by opening the needle valve before its removal from the uterus. When the uterine

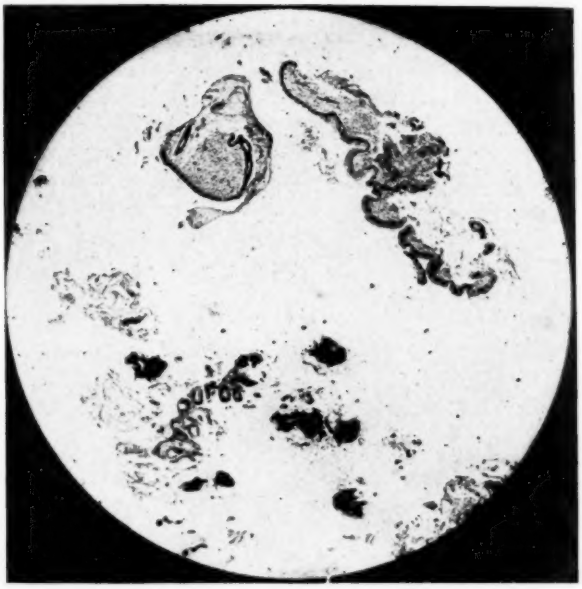

Fig. 2.—Cervix glands and endometrial glands with mucous detritus and small bits of stoma.

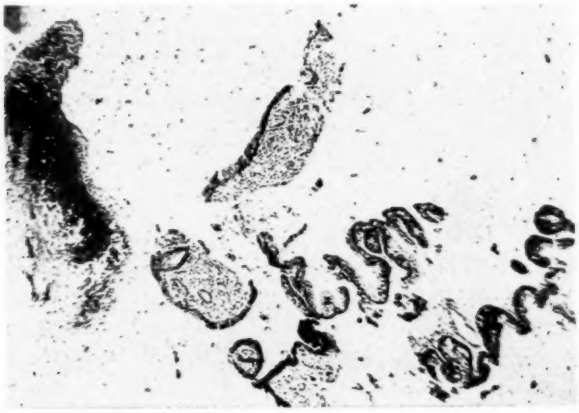

Fig. 3.—Cervix glands and endometrial fragments.

cannula has been removed from the uterus the needle valve is then closed, the rubber tubing is pinched and the pressure is raised to 200 mm. Hg. Then it is suddenly released so that any escape of particles from the cannula can be immediately discovered. This however is very rare. *Considerably more than 200 mm. Hg gas pressure is needed to displace it.* This is accomplished by the hand bulb and solution, the pressure being in excess of 200 mm. Hg. While contained in the uterine cannula the particles of mucosa and mucus moreover offer no barrier to

the steady flow of the gas as can be seen by the pressure dropping to zero the moment the cannula is removed from the uterus. The gas is seen to pass freely through the cannula tip.

In other words the particles are not sufficient in size to obstruct the lumen of the uterine cannula and therefore allow gas to pass alongside them. The tenacious property to mucus besides makes displacement of particles unlikely. When the intrauterine and intratubal pressure reaches 200 mm. Hg the tubes are either sealed altogether or are the seat of high grade stricture. In closed tubes, peritoneal endometriosis as a result of uterotubal insufflation is naturally out of the question.

Transportation via the lymph channels in the sense of the Halban theory[17] may be considered purely hypothetical in connection with tubal insufflation.

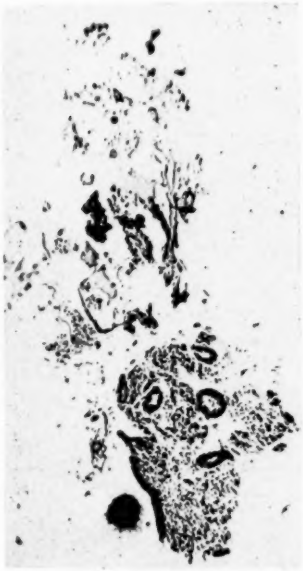

Fig. 4.—Endometrial fragments with mucous detritus.

Fig. 5.—Tiny fragments of stoma cells.

Radiographic pictures obtained after injecting lipiodol into the uterine cavity in over 100 personal cases of tubal obstruction have also proved most valuable in this connection. Except in pathologic conditions as in myomata there is no evidence of blood vessel or lymph channel infiltration by the injected fluid. In none of the other cases comprising the vast majority was there evidence of lipiodol within the "receiving sinuses" in the uterine wall.[18, 19]

CONCLUSIONS

Numerous observations on the clinical use of uterotubal insufflation point to the unlikelihood of endometrial displacement into the tubes and through them into the peritoneal cavity. This presupposes that the method is performed properly and that the mucosa is intact before the uterine cannula is introduced.

Observations of the tiny mucosal particles removed by the uterine cannula and experiments with them in situ within the cannula tip point to the unlikelihood of endometrial dislocation toward the peritoneal cavity.

Gross endometrial trauma as that attending curettage should never be immediately followed by uterotubal insufflation because of an inherently grave danger of gas embolism and of the possibility of dislodging mucosal fragments and blood into the peritoneum. This applies also to menstruation and the presence of abnormal bleeding from the uterus. The amount of endometrial trauma attending the properly indicated and properly performed insufflation at the most favorable time with reference to the menstrual cycle may be said to be negligible.

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POSTOPERATIVE OBSTETRIC EMBOLUS—ITS INCIDENCE, CAUSE AND PREVENTION

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A STUDY of the end-results of surgery within the abdomen or pelvis will usually disclose a certain number of tragic, sudden deaths due to embolism. Odd as it may seem, operations above the diaphragm and below the pelvis are less frequently provocative of embolic death than those abdominal and pelvic procedures which implicate the pampiniform and hemorrhoidal plexuses. Lister states that abdominal incision strongly predisposes to embolism, it matters not what the ultimate object of the operation, and statistics show that thrombosis and embolism are more common in gynecologic and obstetric practice than in other branches of surgery.

In 1712 abdominal hysterectomies at the Mayo Clinic there were five cases of fatal embolism, an incidence of one in 342 cases. In our clinic, in 6266 gynecologic operations there were thirteen fatalities from embolism, an incidence of one in 482.

Morton expresses the view that the special factor concerned *is infection* with a nonhemolytic streptococcus which normally inhabits the female genital tract. In support of infection as a predisposing cause there was a postoperative morbidity of 100 per cent in the cases which make up the basis of this report. Petren's figures which include an analysis of 496 fatal postoperative emboli show that 404 followed abdominal operations upon the uterus, ovaries, appendix and intestines. Strangulated herniae, myomata and pedicle torsions predispose to embolism. No surgical tragedy is so sudden or unexplainable as death from this cause.

ETIOLOGY

The mystery connected with the etiology of thrombosis and embolism makes the subject of great interest to the surgeon. Almost all observers speak of continued blood loss, infection and the consequent change in the blood picture following operation as predisposing causes of embolism. *It is probable that in every surgical patient there is a definitely increased potentiality for intravascular coagulation, from the increase of the blood platelets and leucocytes.* To prove the truth of this statement, Allen of the Mayo Clinic studied the changes in the blood following operation, arguing that since an embolus is a piece of clot dislodged from the tail of a thrombus at some distant location,

attention should be directed toward the mechanism of blood clotting and the factors that might participate in the formation of a clot within a vein following operation. In his summary he notes a constant increase in fibrinogen and a postoperative increase in the number of leucocytes. *Leucocytes are known to furnish thromboplastic substances* which play an important part in the coagulation of the blood; furthermore, there is a sharp prolongation of the prothrombin time which is important, though its significance is obscure, as well as an increase in the number of erythrocytes and the lipoids. Though his study is based on but a small number of cases, it is apparent that *these changes in the blood in response to operation are constant*, and that this nonspecific physiologic response definitely increases the potentialities for

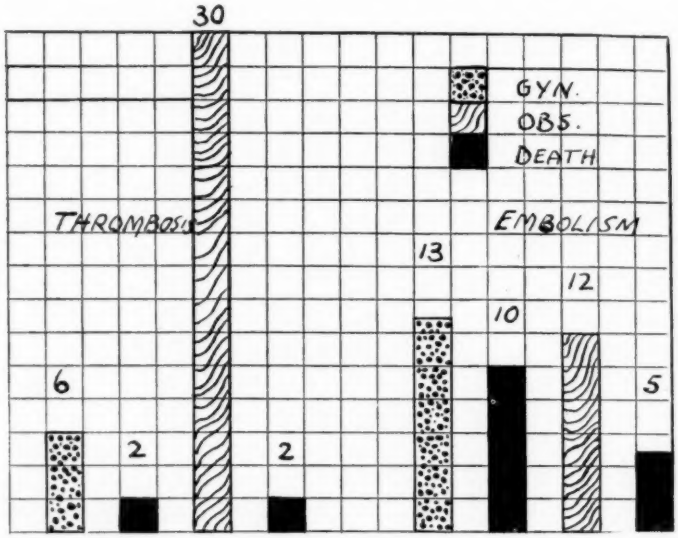

Fig. 1.—Comparative study of cases of thrombosis and embolism in obstetric and gynecologic cases, with mortalities.

intravascular coagulation, hence, may be accepted as a contributing factor. Adding to this the fact that postoperative cases always show some fall in blood pressure with consequent slowing of the blood stream, we have sufficient cause for clot formation. Postoperative thrombosis is a surgical entity which is all too frequent in pelvic operations and may cause pulmonary embolus in the parenchyma of the lung. Fifty per cent of postoperative pulmonary emboli have their source in thrombi of the femoral and iliac veins.

Aeshoff describes five types of thrombosis, each of which may occur in gynecologic and obstetric practice:

(1) Spontaneous (static large veins).

(2) Traumatic (consequent upon ligation or compression of vessels).

(3) Capillary (thrombosis as in transfusions).

(4) Toxic (such as occur in the injections of salvarsan, mercurie, or arsenical poisoning).

(5) Endogenous thrombosis (such as occurs in eclampsia).

Thrombosis, *because it leads to fatal emboli of the pulmonary artery,* represents the most serious complication in abdominal and gynecologic operations. The more we try to obviate the dangerous complications

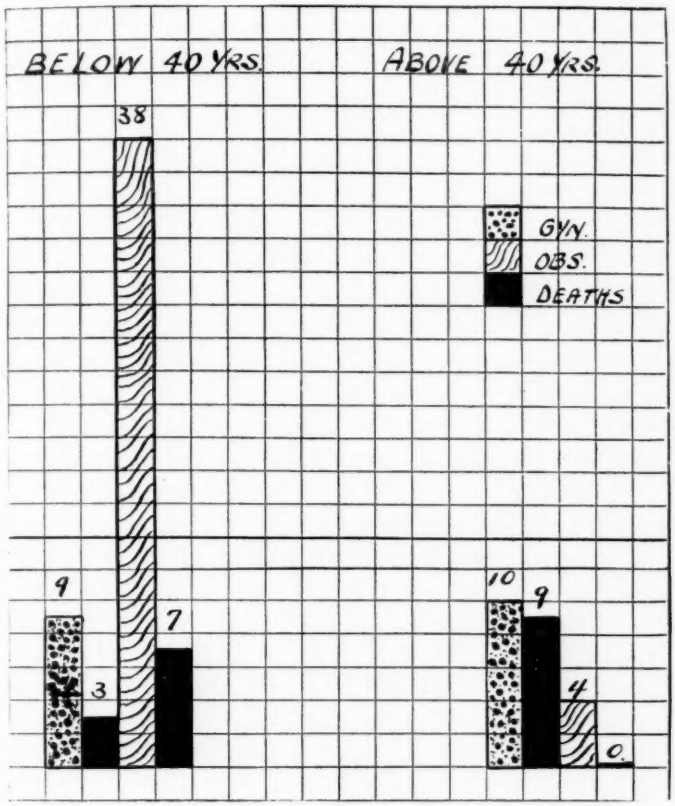

Fig. 2.—Comparative study of cases of thrombosis and embolism with deaths in patients below and above forty years of age.

of embolism the more urgent is our obligation to find out the cause of thrombosis. Mathematically speaking, thrombosis is the function of a number of variables; there is not a single cause, but quite a number of different conditions which are closely related to the occurrence of thrombosis. Among these may be mentioned:

(1) Change in the blood plasma (diminished or increased coagulation).

(2) Changes in the blood elements, resulting in diminished or increased powers in agglutination.

(3) Changes in the blood flow (slowing of the circulation forms eddies which allow the platelets and white blood cells to linger in the periphery vessel where the stream is the slowest—these lay down on the endothelium, a white coagulin from which the thrombus starts).

(4) Changes in the vessel wall itself (endothelial damage).

An analysis of the mechanism of thrombosis shows that sometimes one factor and sometimes another plays the principal rôle. If slowing of the blood stream and alteration of the condition of the platelets are to figure as the direct factors in thrombus formation, we must then consider as indirect factors, changes in the vessel wall, alteration in the cardiac action, and the loss of blood with lowering of blood pressure during and following operation.

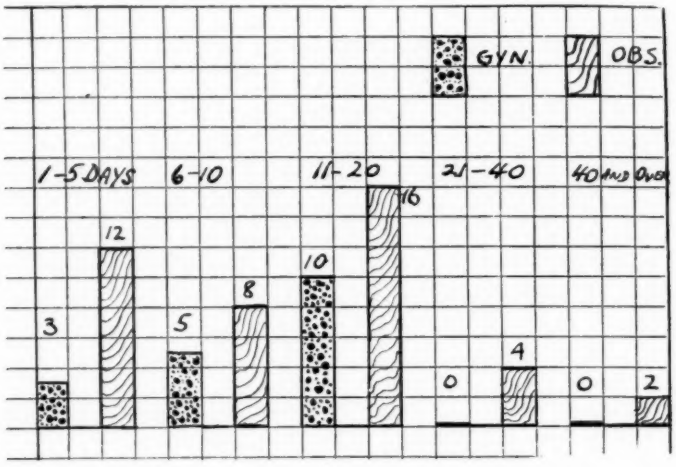

Fig. 3.—Chronologic occurrences of symptoms in 61 cases of thrombosis and embolism.

Snell noted the high incidence of pulmonary embolism in the obese patient who has been subjected to an abdominal operation. Obesity is always a factor in the fifth and sixth decades of life; likewise, obesity tends to make the operation more difficult. There is greater trauma, while mild circulatory failure with resultant venous stasis is more common. Finally, in the obese patient there is a diminished amount of antithrombin. It has been observed that operations in obese women due to the extensive areas of fat which are invaded cause an increased liberation of thromboplastic lipoid substances, such as kephalin and necessarily favor fat embolism.

In a recent paper, Walters shows that many physiologic changes and adjustments follow every surgical procedure. Those which seem to favor the formation of postoperative thrombosis and pulmonary emboli are:

(1) Decrease in the metabolic activities.
(2) Decrease in the rate of blood flow with decrease in blood pressure.
(3) Changes in the cellular constituents of the blood (increase of platelets and leucocytes).

These conditions may be the result of rest in bed without food, interference with the circulation by intraabdominal manipulation and the forty-eight hours of intestinal quiet and muscular splinting of the abdominal wall which follow abdominal celiotomy. These views in the main coincide with the observations of Aeshoff and are more or less confirmed by the clinical study of the authors.

All clinical observers admit that pulmonary embolism is more common in pelvic operations, and in women who are forty or more, who are overweight, inactive and have relatively low pressures; and in subjects in whom there is some degree of postoperative infection, however mild. On the other hand, it has been noted that postoperative

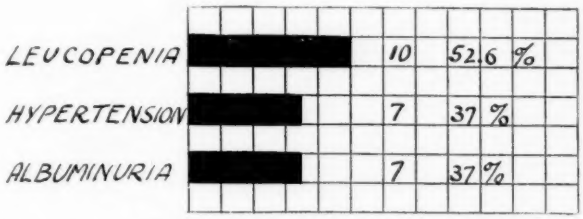

Fig. 4.—Predominating findings in nineteen gynecologic cases of thrombosis and embolism.

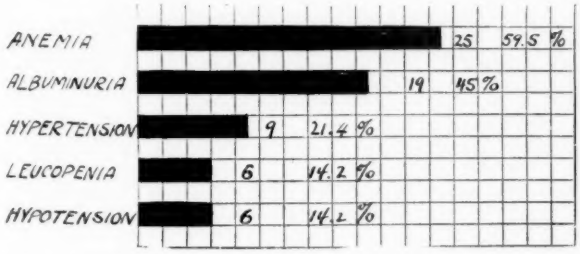

Fig. 5.—Predominating findings in forty-two obstetric cases of thrombosis and embolism.

embolism is uncommon in children, which is probably explained by their activity, age and circulation. Furthermore, Plummer states that in cases of hyperfunction of the thyroid gland, thrombosis and embolism never occur even when the disturbances of the blood from cardiac decompensation are extreme. Solomons calls attention to the great danger in pelvic operations upon women with large varicosities of the legs and thighs, which are only outward manifestations of the pathology which is present within the pelvis.

In our studies of pelvic varicosities, actual disease of the vessel wall has been an almost constant finding, and both experimentally and clinically, *we have observed that a thrombus in a diseased sacculated vein is more unstable than the clot formed in the healthy vein.* Furthermore, that uterine torsion associated with pregnancy or myomata increases the venous distention, adds to the saeculation and favors

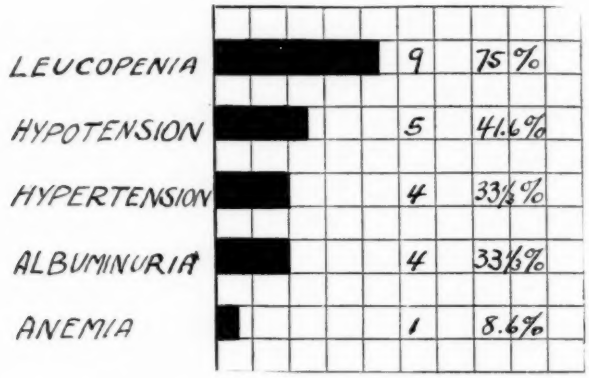

Fig. 6.—Predominating findings in twelve gynecologic fatal cases.

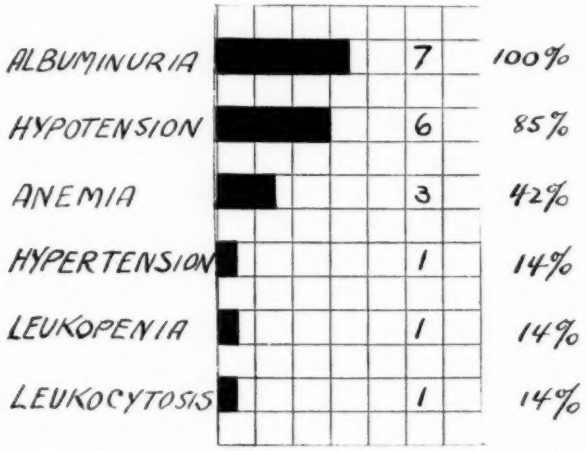

Fig. 7.—Predominating findings in seven fatal obstetric cases.

clot formation. No serial study of myomata associated with pregnancy or with marked torsion fails to show some thrombotic change in some of the nodules. If Walters is right, namely, that the hemorrhage during operation lowers the blood pressure and the extent of the operation calls for physical quiet for several days, we have the usual factors necessary for blood stasis. The authors of this paper have repeated Schenck's experiments on dogs, and we are convinced that stasis without the element of infection does not produce an unstable clot. In support of this conclusion we have studied the effect of aseptic tor-

sion on the vessels of the parametrium, and have proved, at least to our satisfaction, that preoperative torsion distends the vessels, slows the circulation, favors thrombus formation and results in a hypertrophy and hyperplasia of the contiguous tissues.*

In an attempt to clarify and systematize our knowledge we have studied the records of twelve thousand gynecologic and obstetric patients to determine: *first*, the incidence of thrombosis and embolism; *second*, the contributing causes, and finally, we have attempted to draw some conclusions which may be of clinical value.

In this study there were 6,266 women on whom pelvic operations were performed, with 19 cases of thrombosis and embolism, an incidence of 0.3. Among the 5,734 obstetric patients there were 42 cases of thrombosis and embolism, an incidence of 0.72; a total of 61 in 12,000 cases with a gross percentage incidence of 0.5. More detailed

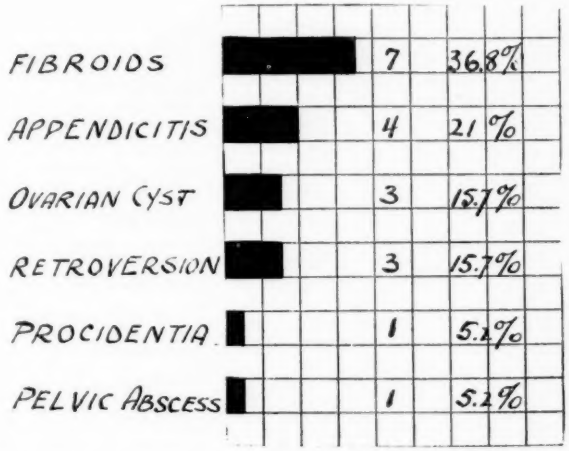

Fig. 8.—Diagnosis in nineteen gynecologic cases of thrombosis and embolism.

study shows that embolism is more common than thrombosis following gynecologic operations, while thrombosis is more frequent in obstetric deliveries, the percentage of embolism in the gynecologic cases being 68 per cent against 29 per cent in the obstetric group. (Table I.) Again, our study shows that the mortality in gynecologic cases resulting from embolism is nearly twice as great as that resulting from embolism occurring in the obstetric patient. Morbidity was a constant factor, being present in the 19 cases which occurred following gynecologic operations, and in the 42 which followed obstetric deliveries.

It is but natural that there are more women below forty who bear children than after forty, hence, there is a greater incidence of obstetric than gynecologic cases with thrombosis below this period. On the

*The results of these studies will appear in a paper to be published subsequently in this JOURNAL.

TABLE I. COMPARATIVE INCIDENCE AND PERCENTAGE OF THROMBOSIS AND EMBOLISM IN 12,000 CASES

SERVICE	CASES	EMBOLISM						THROMBOSIS					
		NO.	PER CENT	RECOVERED	PER CENT	DIED	PER CENT	NO.	PER CENT	RECOVERED	PER CENT	DIED	PER CENT
Gynecologic	6266	13	0.2	3	0.046	10	0.16	6	0.1	4	0.06	2	0.03
Obstetric	5734	12	0.2	7	0.116	5	0.08	30	0.5	28	0.49	2	0.03
Total	12,000	25	0.2	10	0.08	15	0.125	36	0.3	32	0.266	4	0.03

other hand, after forty, there is a marked increase in the gynecologic death rate from embolus, and this coincides with the observations of most authorities.

We further studied these cases as to the time of the appearance of the clinical symptoms of thrombosis and emboli, and found that the occurrence was earlier in the obstetric case. Routine blood and urine studies were done on all of these patients. The outstanding factors were anemia and albuminuria in the obstetric series; while leucopenia, hypertension and albuminuria were more constant in the gynecologic group. These findings seem to point to changes in the blood and circulation together with toxemia as contributing factors which aid intravascular clotting. In the twelve fatal cases occurring in the gynecologic service, 75 per cent had leucopenia. Hypotension was present in 41 per cent of the deaths. Wells states that in anaphylactic shock leucopenia and diminished coagulation time are present. In the presence of passive congestion of the liver we have a similar picture.

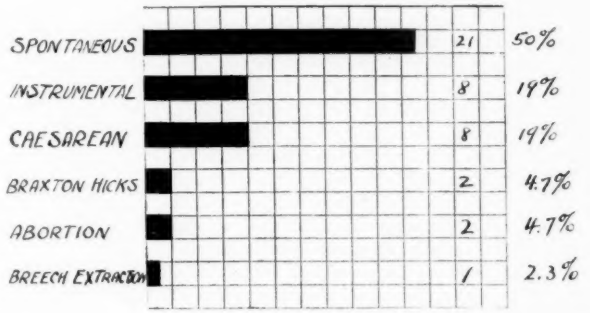

Fig. 9.—Procedure employed in forty-two obstetric cases of thrombosis and embolism.

Some have explained a diminished amount of antithrombin present in these conditions; hence, in the presence of hypotension with venous stasis, intravascular clotting may readily result, especially after the slightest degree of trauma or infection. In the obstetric group of fatalities, albuminuria, hypotension and anemia were rather constant and seemed to be important contributing factors. Again, in the 19 cases occurring in the gynecologic group, fibroids make up 36.8 per cent. The remainder of these cases were diagnosed as retroversion and ovarian cyst. It is a known fact clinically that these pathologic conditions are associated with torsion, varicosities and finally slowing of circulation; hence, venous stasis can also be considered a contributing factor. It is interesting to note that among the obstetric group in which there were 42 cases of thrombosis and embolism that 50 per cent occurred after spontaneous labor; all developed a morbidity and low grade infection. Two cases in this group had been transfused immediately before operation, the indication in each instance being pronounced chronic secondary anemia. Autopsy showed extensive

pulmonary embolism and blood casts in the kidney tubules. Is it possible that transfusion in such a case with cell changes induced, added to the biochemical changes which take place in the blood during anesthesia, precipitated embolism?

SUMMARY

1. The total incidence of thrombosis and embolism in 12,000 gynecologic and obstetric cases was found to be 0.5 per cent. The number of thrombosis in the obstetric group is double the number in the gynecologic. Embolism predominates after gynecologic operations, thrombosis in obstetric deliveries.

2. Thrombosis following operation is more liable to cause embolism than when it occurs following delivery.

3. Emboli following operation are more fatal than those following delivery.

4. The appearance of the clinical symptoms of thrombosis and embolism usually occurs between the second and third weeks, about the time when patients are allowed out of bed.

5. Mortality rate is higher in cases above forty years of age. In our series the number of cases above forty years of age is greater in gynecologic group.

6. Morbidity was found to be present in 100 per cent of cases; infection is therefore a factor which must be considered.

7. Obesity, hypotension, leucopenia, albuminuria, pregnancy, age, fibroids, anemia, toxemia—all predispose to venous stasis.

8. Experimentally, torsion leads to varicosities, stasis, and thrombosis with a generalized hyperplasia and hypertrophy of all contiguous tissues.

CONCLUSIONS

1. Venous stasis, the physiologic blood changes following operation, trauma, and infection, are the chief factors which predispose to thrombosis and embolism.

2. A more thorough preoperative study with detailed medical treatment of cases with hypotension, low basal metabolism, leucopenia, anemia and hypertension may lower the incidence.

3. As a prophylactic measure to diminish the occurrence of femoral thrombosis, besides asepsis and antisepsis, we must increase the metabolic activity and provide for the proper circulation of blood in the lower extremities. This can be accomplished by the employment of passive motion and the administration of thyroid extract before and following operation.

4. The subject of thrombosis and embolism is far from being settled and still remains an important problem for investigation.

20 LIVINGSTON STREET.

FETAL MALFORMATIONS IN MULTIPLE PREGNANCY

By Fred L. Adair, M.D., Chicago, Ill.

(From the Department of Obstetrics of the University of Chicago)

HUMAN and other twins have been studied by various investigators in an effort to gain more light on various problems associated with heredity. The importance and significance of such investigations have not been generally realized, especially by those who are active in the practice of obstetrics. They are in a peculiarly advantageous position for the study of some of these interesting and important questions which are related to human twinning. The obstetricians can observe the fetal changes associated with abortions, miscarriages and premature births and also those cases where one of the twins dies as a result of some defect of development or other affection.

It is usually possible to determine by an examination of the placenta and membranes whether the twins are monochorionic or dichorionic, which ordinarily means that the twins are monozygotic or dizygotic. This is not absolutely true as dizygotic twins may be monochorionic due to a fusion of the two sacs. The observation of the amnion is of importance as there may be only one in monozygotic though there are usually two. In instances of fused twins there is always only one amnion. It is of importance to examine carefully the placenta as a double or fused placenta speaks for dizygotic twins while a single placenta is often dizygotic. The cord is always double in dizygotic but may be more or less completely fused in monozygotic twins.

In looking over the reports of various interesting cases in the literature, and in checking the hospital records of some unusual conditions occurring in association with multiple pregnancy, one cannot help being struck with the incompleteness of the information regarding some of these points.

It is well known, of course, that duplicate or identical twins are always of the same sex and that fraternal may or may not correspond in this regard. Ratios and data given by Nichols and others and quoted by Newman indicate that the ratio of male twins, to mixed twins, to female twins is 1:1:1. If all were dizygotic, this proportion should be 1:2:1, with predetermined sex. This indicates, according to Newman, that "nearly half of all the same sexed twins are monozygotic and hence morphologically stand for but one individual to the pair." He is of the opinion that about one-fourth of all human twins are monozygotic.

This point could be pretty definitely settled by careful routine observation of placenta, membranes and cord. It is partly the lack of this information which has led Galton, Wilder, Siemens, Newman and others to set up schedules by which they seek to determine whether the twins are fraternal or identical. They have, of course, also been interested in determining of what the identity consists and how complete is the real duplication which may be symmetrical or of the image or mirror type.

On the basis of intrauterine data O. Schultze (according to Newman) divided twins into four categories which have been quoted by Wilder.

1. Twins with two blastodermic vesicles, two deciduous reflexae, and two placentae, which probably originate from two separate ova.

2. Twins with two separate blastodermic vesicles inclosed in a single decidua, but with two placentae and sets of umbilical vessels and with fused chorions. They apparently originate from two ova.

3. Twins with two amnions and two umbilical cords meeting near the center of a single placenta. They are enclosed in a single chorion and amnion. They are always of the same sex. Various possible explanations are offered and it is concluded as improbable that the duplicate twins would arise from an ovarian egg with two nuclei. It is suggested that the two probably arise from the complete separation of the two blastomeres which result from the first cleavage of the fertilized egg.

4. Twins resulting from conditions as above when the blastomeres are close together and a common amnion results and fused twins develop.

Newman is of the opinion that there are really only two types of human twins, the fraternal or dizygotic and the duplicate or monozygotic. He further believes that in humans twinning is variable and begins earlier in some than in others and becomes more complete. The double monsters are probably monozygotic twins in which the twinning process begins later than in separate twins and is never fully completed.

In making this presentation to the members of the American Gynecological Society, the main purpose is to make use of available information regarding malformations occurring in multiple pregnancies to determine the question whether fetal malformations are the result of conditions present in the ovum when fertilized, or the consequence of intrauterine environmental conditions.

Among 25,000 deliveries at the Chicago Lying-In Hospital there were 354 twin pregnancies, a ratio of about 1:70. Among these twins seven malformations are recorded which is a percentage of approximately 1.98. There were 568 listed deformities among the single pregnancies which yield a percentage of about 2.3. There would seem to be no material difference in the incidence of deformities in multiple and single pregnancies, at least not among those which go on to the period of viability.

Of these seven twins with malformations and other affections three may be considered as definitely dizygotic inasmuch as there was a double placenta in each case. Only one of the twins was affected in all of the instances.

CASE 1.—Mother para ii. Twin No. 1. Female, Weight 3810 grams. Alive. Twin No. 2. Sex not determined. Fetus papyraceous with its placenta. The degenerated fetus was surrounded by its complete membranes. The fetus itself showed some evidence of being a monster with a meningocele, spina bifida, and deformity of the head.

The placenta of the dead fetus was small, degenerated, and adjacent to but separated from the placenta of the living infant. (34749) Dichorionic.

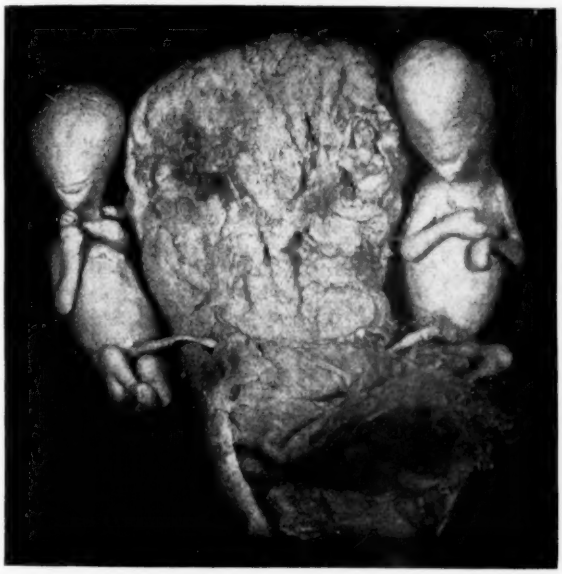

Fig. 1.—Case 8. Shows deformed twin fetuses with a common sac.

CASE 2.—Mother (60912) para i. Twin No. 1 (61745) male, weight 1140 grams. An anencephalic monster with a spina bifida. There was a polyhydramnios of about two and one-half gallons. Twin No. 2 (61746) male, weight 1960 grams. There was a slight tongue tie but otherwise it was normal and survived. The placenta was double but fused, and there were two chorionic sacs. Dichorionic.

CASE 3.—Mother (73746) para iv. Twin No. 1, macerated fetus. Sex undetermined. Weight 345 grams. It was born before the mother entered the hospital. Its placenta was delivered before the birth of Twin No. 2, male, weight 2325 grams. Living. Dichorionic.

CASE 4.—Mother (22520) para i. Twin No. 1. Female, weight 2115 grams. Rudimentary left hand with thumb and some fingers missing. Twin No. 2, female, weight 1380 grams. A normal premature infant. The placenta was single with two separate cords. The records are not clear as to whether these were mono- or dichorionic twins.

CASE 5.—Mother (46276) para i. Age 21 years. Gestation 32 weeks. Twin No. 1. Female, weight 1180 grams. Lived 10 hours. A monster with a cephalo-

meningocele. Twin No. 2. Female, weight 1135 grams. Normal development but premature and lived seven hours. The placenta was single with two cords. The record does not establish whether or not these twins were mono- or dichorionic twins.

CASE 6.—Mother (61986) para i. Twin No. 1. Male, weight 2725 grams. Normal, lived. Twin No. 2. Male, stillborn and macerated. Hydrocephalic but an autopsy revealed no other malformations. Placenta was single with two cords. One portion of the placenta was degenerated. The record does not establish the character of the twins.

CASE 7.—Mother (66432) para iii. Twin No. 1. Female, weight 3050 grams. Diagnosed as Mongolian idiot. Lived. Twin No. 2. Female, weight 3655 grams. Normal, lived. Placenta and chorion not described.

There are also in my series eight other cases of malformations in twin pregnancies. These have been collected from various sources so that it is difficult to give any statistical data as to the percentage incidence of either the multiple pregnancies or the malformations.

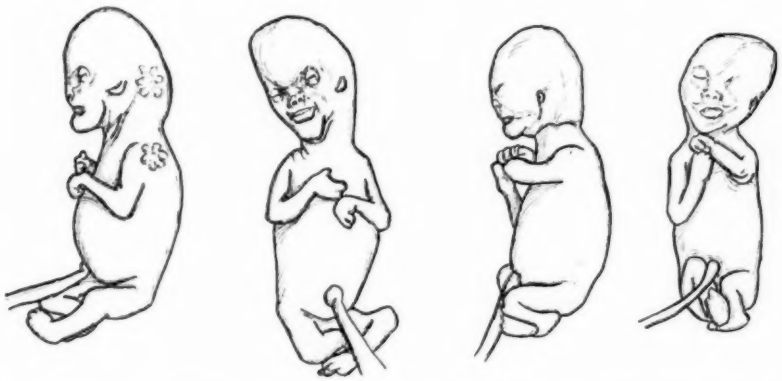

Fig. 2.—Case 8. Drawing made from the same fetuses to show similarity in deformities, especially of the face and extremities.

CASE 8.—Specimen from Dr. J. E. Hynes of Minneapolis.

Mother grav. i. Hyperemesis but no evidence of genital infection or tumors. Last menstruation Feb. 2, 1915. Spontaneous abortion on June 18, 1915. The twins were smaller than the menstrual age indicates. Twin pregnancy with similar deformities of both fetuses. The faces and extremities were both deformed in a similar manner, the similar loss of digits on the hands and feet of both fetuses being quite similar. Their crown rump measurements were 51 and 53.3 mm. respectively. The twins appeared to be of the same sex and had a common chorionic sac but two amniotic sacs and two cords. Unfortunately, the specimen was lost before serial sections were made for microscopic study. They were monochorionic and doubtless monozygotic twins.

CASE 9.—B-3939. Private patient. Grav. i, para i. Last normal menstruation Jan. 28, 1924. Date of confinement Sept. 27, 1924. Menstrual age 35 weeks. Mother has had a normal pregnancy and delivery of a normal male infant at term. Twin No. 1. Male. Normal except for some hypospadias. Twin No. 2. Male. Normal except for some hypospadias. The hypospadias was nearly identical in both twins. The placenta was single with a double amnion and a single chorion. There were two umbilical cords both with marginal attachments.

CASE 10.—Source from a series of autopsies. A24-260. Mother 21 years old, para i, menstrual age about seven months. No lues. There was hydramnios of Twin No. 1, which was a female premature and anencephalic. Twin No. 2 was a normal premature female.

The hospital record described a single placenta weighing 700 grams with a single chorion. The infants were considered to be identical twins.

CASE 11.—Source from a series of autopsies. A26-398. The mother was 29 years old. Para ii. Wassermann negative. Twin No. 1 was a premature female of about 32 weeks' gestation. There was hydramnios and the infant was an anencephalic macerate. Twin No. 2 was a female, premature, living infant. The placenta was described as double with a small one for the second. Dichorionic.

CASE 12.—Mrs. M. P. M.G.H. No. G1366, age 32. Para v, grav. vii. No. 22621. Aborted twins about six months' gestation. Twin No. 1. Male, no anomalies, died of prematurity. Placenta small, normal cord 30 cm. long. Twin No. 2. Female with craniorachischisis with a velamentous attachment to the placenta. These were dichorionic twins.

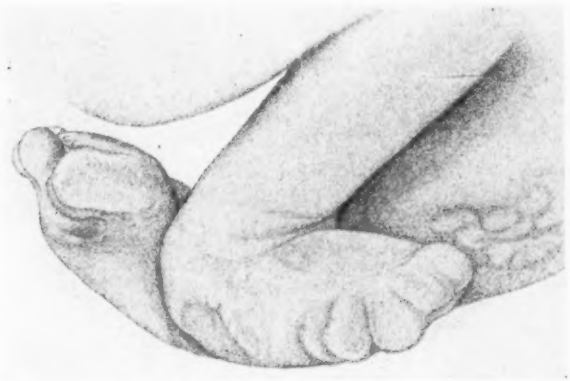

FIG. 3.—Case 8. Feet of one fetus showing deformity involving a foot and digits.

CASE 13.—Case of Dr. P. L. Owen. Mother para iii, grav. iv. Age 33 years. During seventh month of gestation had diphtheric vaginitis. Considerable distress during the latter part of pregnancy with insomnia. Marked distention of abdomen. Triplet No. 1 was female. Delivery spontaneous O.D.A. Birth weight about 2 pounds. Fetus had separate membranes. Lived four days. Triplet No. 2 was female, birth weight about 5 pounds. Diecephalic. Had separate membranes. Delivered by forceps. Respiration on both sides. There were two heads and two necks with two trachea. No external evidence of other deformities. Died shortly after birth. Triplet No. 3 was a female, delivered by breech extraction. Birth weight 5 pounds. Separate membranes. Placenta of very large size. There appeared to be three separate placentas, two of which were normal, more or less fused. The third was completely separated. There was a separate cord for each child. Lived for some time after delivery. Case of trichorionic triplets with fused monster.

CASE 14.—Fused twin from a series of autopsies. (Diecephalus.) Mother para i. Age 23 years. Delivered at term. Infant had two heads. Birth weight 3276 grams. C. H. 48.5 cm. Two vertebral columns. There was a single sternum. The extremities were symmetrical. Defect of right diaphragm permitted the appendix and

intestines to rise up into the plural cavity. The heart showed two ventricular masses with two rudimentary auricular appendages on the right and one on the left. There was a tendency to a duplication of liver lobes with an absence of the gall bladder and ducts. There were two stomachs and some tendency to a duplication of the intestines. Two thymic glands. The placenta weighed 560 grams. The cord was 22 cm. long and showed a central attachment.

CASE 15.—Private case, Mrs. P. Grav. vi, para iv. Last normal menstruation June 26, 1917. Delivered March 4, 1918. Twin No. 1. Female, birth weight 3120 grams, 49 cm., cleft palate and harelip. Thirty-seven weeks' gestation. Twin No. 2. Male, 3315 grams, 49.5 cm. Normal infant. Both cephalic presentations. Placenta was double with two placentas entirely separate. Case of dichorionic twins.

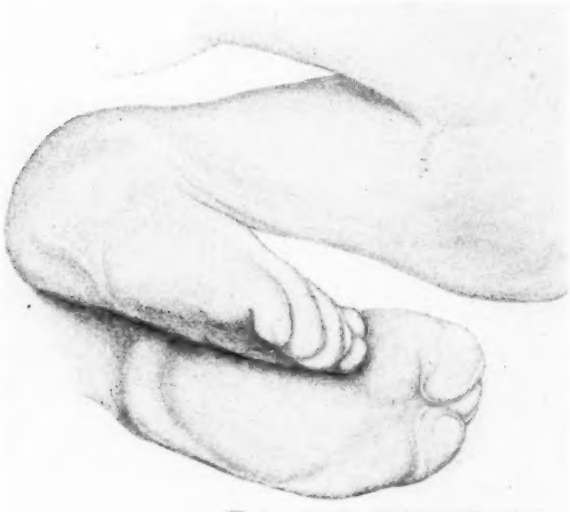

Fig. 4.—Case 8. Feet of the other fetus showing similar deformities.

CASE 16.—Mrs. J. B. Private case. B4086. Grav. i, para i. Last normal menstruation March 28, 1924. Due Jan. 7, 1925. Delivery Jan. 1, 1925. Twin No. 1. Female, O.D.A. Alive and mature. Twin No. 2, female, breech extraction. Alive and mature. Number one had club foot. Placenta double with two chorion and two amnion sacs. Case of dichorionic twins.

CASE 17.—Mrs. G. M. Case of Dr. Haggard. G.21-82. Mother para i. Aged 18 years. Pregnancy of about two months diagnosed on May 4. On July 5 patient was sick in bed with nausea, abdominal pain, and uterine bleeding. Improved after five days. Blood pressure and urine were normal. In December she was delivered of normal infant. The placenta was that of a multiple pregnancy—one-half was normal. The other portion showed a fetus compressus lying in a sac of its own on the white, firm, fibrous, and degenerated portion of the placenta. The fetus shows well-developed skeletal structures on x-ray examination. The C.R. length was 15.5 cm. The estimated menstrual age was 19 weeks. Microscopic examination of the placenta showed normal tissue for the living infant and marked degeneration for the dead premature fetus. They were probably dichorionic twins but one could not be absolutely certain of this point.

These cases have been collected from various sources in a somewhat haphazard manner without the present thesis clearly in mind. The data are presented here to stress the importance of careful observation of multiple pregnancy in determining some of the facts with relation to heredity and also with reference to the particular theories regarding the causation of malformation, chiefly from the standpoint of the germinal versus the intrauterine or environmental origin of these conditions. In order to secure some further information some of the literature has been investigated for case reports of malformations in multiple pregnancies. There is much in the literature concerning diseases, neoplasms, etc., which occur in twins not only in fetal, infant

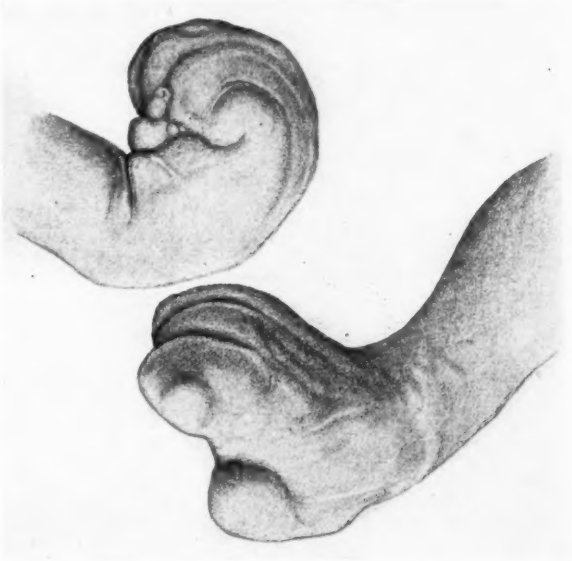

Fig. 5.—Case 8. Shows deformities involving the hands.

and child life, but also in adult life. Some of the relationships are peculiar and striking but will not be considered at this time.

It should be borne in mind, according to most observers, that duplicate twins are not identical in all the minutiae. Galton was the first to make definite attempt to determine the degree of identity in human twins and suggested the use of the patterns of friction ridges on the palms and soles. Wilder carried out this study in detail. Newman feels that he goes too far in eliminating certain variations in monozygotic twins. He points out that there are very definite variations in the two sides of the same individual and that we could not expect complete identity in two individuals of monozygotic origin when there are definite differences in the two halves of the same organism. This should not be used as an argument against heredity as there must be

some inequality of distribution of determinative factors during the various cleavages. Siemens has stated that "approximately the same external influences work upon each partner of twins and that the lesser similarity of fraternal twins in comparison to that of duplicate twins must originate in the hereditary 'anlage' and is as a result an index of the hereditary character." Leven has commented that "we have even in duplicate twins no complete identity, but only the greatest known approximation to such a condition."

Birkenfeld quotes from Bauer, "If we find similar morbidity in single ovum twins and are able to eliminate identical external conditions as etiologic factors or exclude accident, then it proves with all the

Fig. 6.—Case 8. Shows deformity of the face of one fetus.

necessary clarity and certainty the significance of the latent predisposition to disease in the individual germ plasm."

Birkenfeld wished to determine whether or not harelip and cleft palate were inheritable conditions and studied 204 cases among which there were eight pairs of twins of which three were of different sex and five of the identical sex. Of the first group both twins, male and female, were affected in only one pair. In four of the five pair it was not possible to determine whether or not the twins were identical. In one set they were identical and had harelip and cleft palate one on the right and the other on the left side. The author has collected eight similar cases of uniovular twins. In most it was of the image or mirror type and in only one pair was the defect on the corresponding side. Case 14 in the present series was of dichorionic twins of opposite sex in which the female infant had a harelip and cleft palate, the male being normal.

There are quite a number of cases in the literature of twins with malformations of the head and spine. It is not my intention to consider all of these but only some which resemble the types encountered in our own series which were of the anencephalic cranioracheschisis type. These cases seem to occur in both the mono- and dichorionic twins. Among those who have reported dichorionic twins with anencephalic deformities are Hann, who cites one case with hydramnion and a normal premature female born alive and a male twin with anencephalus born dead. It also had rudimentary extremities. There was a single placenta and one chorion with two amniotic sacks. This is monochorionic but must be dizygotic as the twins are not of the same sex.

Michel has also reported a case of Bonnaire of binovular twins in which the first-born was normal. The second had hydramnios with encephalocele and defective vertebrae. The author states these were binovular twins.

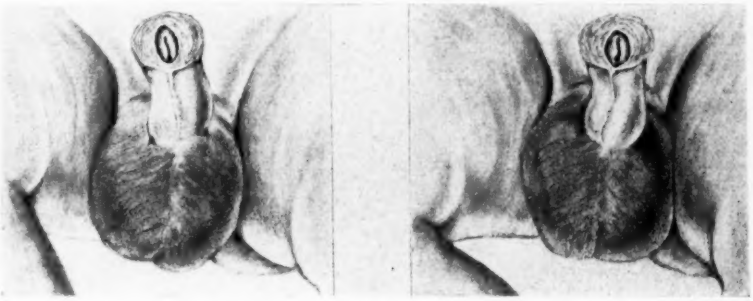

Fig. 7.—Case 9. Drawings from twins showing identical deformities—hypospadias in monochorionic twin fetuses.

Kosmak has also reported a case of dichorionic twins of the same sex (female) having two distinct placentas and sacks. The first-born was normal. The second had hydramnios and was an anencephalic monster.

Foster and Carson have described an unusual case of a multiparous woman about five months pregnant who gave birth to quintriplets after induction of labor. There were three normal female fetuses, one anencephalic fetus and the fifth was a pathologic embryo. All four were females. There were four amniotic sacks with four well-developed cords and a poorly developed fifth attached to the embryonic mass. The statement is not clear as to the chorionic character of these fetuses. There are some reports of monochorionic twins. Lewis has described uniovular twin males with a common placenta and chorion but with two amnions and cords. It was from a first pregnancy and the result of a premature labor. The living male was normal and born first. The second male was of the anencephalic type.

Abelen has also described a case of monochorionic twins of 29 weeks' gestation. The mother had one normal child living. The first of twins had a hydramnion, but there was little amniotic fluid with the second. Both showed signs of life for a few moments after birth. They showed like deformities, both having large spina bifida in the lower lumbar regions, complete eventratio abdominalis, double sided club feet, and nondevelopment of the external genitalia. One had a cystic kidney.

In our series there are four anencephalic monsters, Cases 2, 10, 11, and 12. Of these three are dichorionic and one is stated to be monochorionic. In all of them only one of the twins was deformed. Hydramnios is stated to have occurred with the deformed twin alone in three of the cases. In the fourth there appeared to be no hydramnios. Case 5 was probably dichorionic with one twin showing a cephalomeningocele; the other twin was normal. Case 6 was hydrocephalic and probably dichorionic with only one twin affected. There is no case in which both twins are affected except the case described by Abelen.

The constant association of hydramnios with the monster twin is certainly suggestive of the fetal origin of this condition. It is not surprising that only one fetus is affected in dizygotic twins though one might expect to occasionally find both of them deformed if heredity is a factor. In monozygotic twins one should find similar deformi-

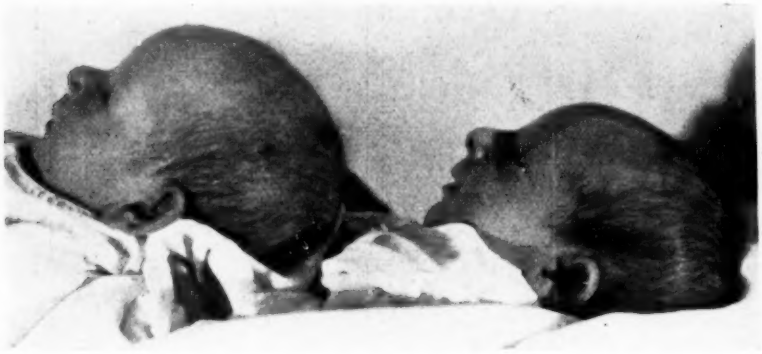

Fig. 8.—Case 16. Shows a dissimilarity in facies of dichorionic twins, one of which had a club foot.

ties in both if it is of germinal origin, though it is conceivable that the cleavage of cells might not always be equally perfect.

It should also be borne in mind that the observations may have been insufficient to establish the diagnosis of uniovular or binovular and that monochorionic is not the necessary equivalent of monozygotic.

There are three cases in the series with deformities of the extremities. Case 4 with a rudimentary left hand and with the thumb and some fingers missing. This was not certainly a case of dichorionic twins.

Case 8 fetuses with malformed heads and symmetrically deformed upper and lower extremities. These fetuses were monochorionic twins.

Case 16 dichorionic twins one of which had one club foot of the talipes calcaneo varus type. Smilga in 1896 reported a case of twins which he considered binovular because of the double placenta and sack. The twins had similar deformities. He now believes them to

be identical as they conform to Siemens' schedule. The deformities consisted in No. 1 twin of an ankylosis of both knee joints with double genu recurvatum and talipes varus; in No. 2 twin there was also a talipes varus with a left genu recurvatum and ankylosis. The mother gave a history of having been born with a club foot.

Berkheiser reports a case of twins with unilateral symmetrical talipes equino varus. Both were females aged twenty months when first seen by him. He does not state whether or not they were identical twins. One cousin had a similar deformity. He found only four cases of bilateral congenital talipes affecting both twins cited in the literature. It would be interesting to know about twins with club feet. The similarity of the deformities in the twin fetuses (8) is certainly striking and strongly suggests a common origin. The absence of a symmetrical deformity in the dizygotic twins (16) argues against environmental cause.

Case 9 is very interesting as the deformities are almost identical in these twins where the evidence points definitely to monozygotic origin. I have found no citations in the literature of similar cases.

Case 7 is of considerable interest though the dichorionic character of the twins is not established. There is considerable literature on this subject which points to the hereditary character of mongolism. Strictly speaking this condition could not be considered a malformation but it is certainly due to defective development. McLean was one of the first to write of mongolism in twins. He saw these twins when they were six and one-half months old; one was a normal female and the other a male Mongolian idiot. These were the offsprings from the fourth pregnancy. The previous children were normal. The difference in sex points clearly to dizygotic twins of which only one was afflicted. Armstrong reports a similar case but with insufficient data.

Shattuck also cites a case of his own, one female twin was a mongol and the other a normal male. Other children of these parents were normal. One of the two dizygotic twins was affected.

Halbertsma reported a series of cases and stated, "The conclusion that mongolism is germinal in origin is deduced from the fact that mongolism occurs in one of twins. An examination of these cases reveals that all have resulted from a two egg pregnancy. Cases of mongolism in both twins of different sex are unknown; of like sex, there are cases described, which is in accordance with the theory that mongolism has to be regarded as the result of defects inherent in the germ plasma."

Mitchell and Downing have gone through the literature and included in their article many reported cases and add one to their own in which one male was a mongol and the other was normal. They were followed until 14 months of age, when the mongol died. At birth there was a double placenta, chorion, and amnion. They summarized that "These facts are in favor of the theory of mongolism being a germ plasma defect and are against any theory which holds that causes operative during

pregnancy are at fault." "In no case has it been demonstrated that mongolism can occur in one of twins, the result of a single ovum pregnancy." In addition there are some reports of monochorionic twins where both were affected.

Strauch cited a first pregnancy with twins which he considered duplicates where both were mongols. Orel collected 32 cases of mongolism in twins from the literature and added two of his own. In four cases the sex was not stated. In the group of twins of opposite sex never more than one was affected. In those of the same sex four pairs had mongolism and only one of the twins had this defect in the remaining pairs. The author believes mongolism to be hereditary. Reuben and Klein review some of the literature and report a case of male twins apparently identical. Both had similar diseases at corresponding ages and both had undescended testicles. Finger prints and x-rays of both correspond. Both of these twins were mongols. The evidence from the case reports in the literature seem to indicate with some certainty that of dizygotic twins only one is ever affected with mongolism and that in monozygotic twins both are affected.

There are three cases in our series which should probably not be included among malformations as they doubtless result from fetal deaths and partial absorption. This could be more properly considered as an environmental condition which could arise with either a monochorionic or dichorionic twin.

Case 1 presented evidence of being a fetus compressus and a monster as well in dichorionic twins.

Case 3 a fetus papyraceus in dichorionic twins.

Case 17 a fetus papyraceus in which it is not certainly dichorionic. Mall has described binovular embryos in which there was a normal embryo of about three weeks on one side of the chorion and a well-developed umbilical vesicle on the other side. This is somewhat different from the fetus papyraceus but is of interest in this connection.

Mosher reported a case of fetus of about five months' gestation with the delivery of a normal infant at term. Single placenta with two cords inserted at its periphery. Two amnions. He states there are 88 cases in the literature. Normal female delivered at term to multiparous woman. Placenta came spontaneously and had incorporated in the membranes of the first twin a papyraceus fetus about 16 cm. long and a degenerated placenta attached to the fetus papyraceus by a degenerated cord. This fibrotic placenta was about 6 cm. in diameter. This appears to be a case of dichorionic twins. There are also two curious cases reported of triplets with two of the fetuses as papyracei. Wolff has cited one of these and Moss the other. In the former case the normal infant had a separate placenta and the two papyracei were duplicate twins with a single sack. The latter also delivered a normal infant with its own placenta. The papyracei had a bilobed placenta with a common sack.

Ayora describes a case of female monochorionic fetuses, one edematous probably from strangulation of the cord, and the other a fetus papyraceus. It would seem that this condition could develop in either monochorionic or dichorionic pregnancies from causes which produce fetal death in one twin without bringing on a premature labor or causing the death of the other.

There are two cases of fused twins which must be monozygotic. These are 13 and 14. Fused twins are not commonly seen but are well known and there are many varieties.

Case 13 is unique and Dr. Owen gave me the description but did not have as good an opportunity to study the placenta as he wished. It amounts to quadruplet with a trizygotic multiple pregnancy. The fused twins are monozygotic and each of the other two fetuses seem to have had their own placenta and chorion. It would be difficult to account for such a combination on anything except a defective duplication of the germ plasm. The other fused twin is mentioned as a case to illustrate the result of incomplete or possible late cleavage. It would not be at all difficult to imagine two complete monozygotic individuals as a result of an earlier and more extensive cleavage of fertilized ovum.

As a result of this consideration one might state that we should make a more earnest effort to determine at the time of birth whether the infants in multiple pregnancies are monozygotic or dizygotic. This can be done by comparing the twins and noting the points of similarity, by examination of the placentas for separation and lines of cleavage to determine whether or not it is a single placenta or in reality two fused placentas. The examination of the membranes is important especially in the partition between the two sacks. One can often determine whether or not there are two or three layers and thus decide if it is a monochorionic or a dichorionic pregnancy. The observation of the cords is also of importance as this may give one suggestive evidence of one or two placentas.

The study of diseases and conditions affecting the intrauterine life of fetuses would be definitely enhanced by such observations which would ultimately prove whether or not certain affections are inherited or acquired and of germinal or environmental origin. Dizygotic twins might conceivably have the same unusual condition, but one would hardly expect two such ova to be fertilized at the same time. Environmental conditions should affect both more constantly. Monozygotic twins should have similar conditions develop as the result of cleavage of the same ovum or if one considers a double nucleus as the etiology of twins the result should be similar. One could not expect these changes to be uniformly and constantly identical. Environmental conditions should act upon monozygotic twins in about the same manner as upon dizygotic except they might be more nearly equal in their susceptibility to various externals because of their greater similarity.

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GRANULOSAL-CELL TUMORS OF THE OVARY AND THEIR RELATION TO POSTMENOPAUSAL BLEEDING

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TUMORS of the ovary having a tendency in their growth to the formation of structures resembling graafian follicles have been the subject of considerable interest in the German literature for many years. Since v. Kahlden's case of "Adenoma of the Graafian Follicle with Transition to Carcinoma" was reported in 1895, numerous investigators have given us more or less similar cases. R. Meyer, R. Schröder, Krompecher, Neumann, Scheyer, Blau, Glockner, Voigt, Tietze, Mullerheim, Isbruch, Aschner, Gottschalk, and others, have all reported cases of this group of tumors. Judging from the histologic descriptions and photomicrographs of these cases, it would seem that we are dealing with a group of tumors closely related, but not identical, having in common one characteristic, a tendency to the formation of structures resembling the graafian follicles. Histologically, there are variations in structure on the basis of which different authors have subdivided the group into specific types. Various names have been applied to these allied tumors, such as adenoma of the graafian follicle, folliculoma ovarii malignum, carcinoma folliculoides, oöphoroma folliculare, and granulosal-cell tumors. Meyer has divided the granulosal-cell tumors into the folliculoid and cylindroid, both structural types frequently being present in the same tumor. In the American literature, I have found only three cases, the first reported by M. Robinson in 1923 and the other two by E. S. J. King, in 1929. There is little doubt but that we are dealing with a group of the rarer ovarian growths, and it is my belief that the tumors are more frequent

than might be supposed from the relatively small number of cases reported in the literature for, since our first case in 1926, we have encountered three others. The fact that these tumors have failed to attract the attention of American gynecologists is particularly remarkable, for no ovarian tumors are more interesting histologically and histogenetically. From a clinical point of view they also deserve recognition because of their frequent association with postmenopausal bleeding, a symptom upon which more light may be cast with much profit.

The following three cases of granulosal-cell ovarian tumor illustrate the characteristic history of these neoplasms.

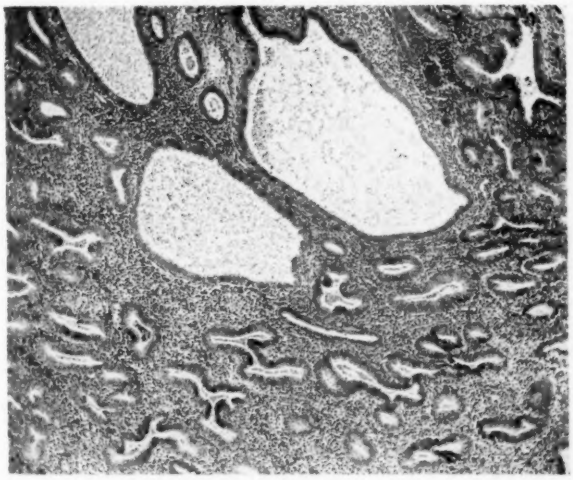

Fig. 1.—Endometrium of Case 1. Note the abundance of glands and great variation in caliber of the glands, showing the typical "Swiss-cheese" pattern characteristic of hyperplasia.

CASE 1.—Mrs. M. F., aged sixty-five, complained of vaginal bleeding. The menstrual history prior to her menopause, 22 years previously, was entirely normal. She was married at twenty-four and had had five full-term pregnancies. The oldest child was forty-one, the youngest twenty-three. Six months prior to coming to us she had bled for a few days, the first time since her menopause. Since this time she had bled for a few days approximately once a month "about as profusely as a normal period."

The patient was a very well-nourished woman. Hemoglobin 75 per cent, but the general examination otherwise of no special interest. Pelvic examination showed a uterus rather large for the patient's age. Cervix transversely lacerated but otherwise normal. To the right of the uterus was a soft mass about the size of a small orange. The left ovary was not felt.

Operation.—Dilatation and curettage was first done. The curettings showed no gross evidence of malignancy. A supravaginal hysterectomy, double salpingo-oöphorectomy was done. The patient made an uneventful recovery and is well four years after operation.

Pathology.—Gross: The supravaginally amputated uterus was larger than normal for the patient's age. It measured $10 \times 8 \times 6$ cm. There were two very small intra-

mural fibroids. The endometrium was considerably thickened and ragged, no doubt as a result of the curettement which had preceded the hysterectomy. Both tubes were normal. The right ovary was enlarged to form a tumor 8 cm. in diameter. It was soft and spongy, evidently being partly cystic. The surface was smooth and free from adhesions. On section the tumor was honeycombed in structure and

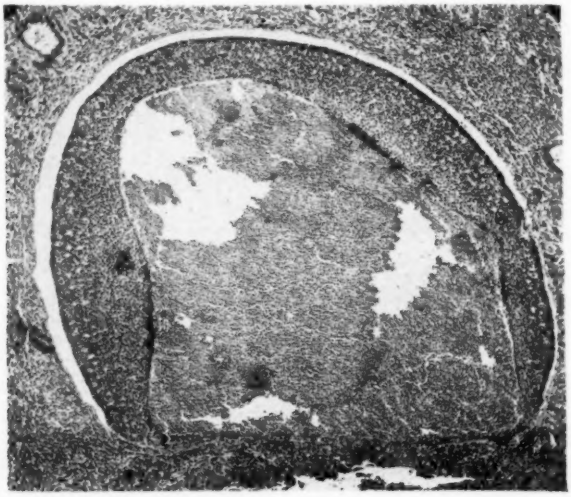

Fig. 2.—Moderate-sized follicle from Case 1. Note the broad zone of granulosal-like cells surrounding the cavity which in this case contains blood.

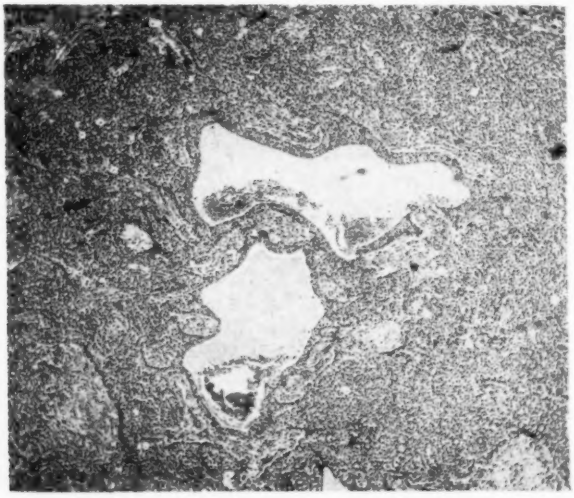

Fig. 3.—Two smaller follicles from Case 1. They contain an eosin-staining homogeneous substance containing some blood and cellular débris.

blood and straw-colored fluid poured out. The cysts varied in size from 3 cm. to just within the range of visibility. The left ovary was a normal senile structure.

Microscopic: The endometrium was much thickened. There was a great increase in the glandular elements and a great variation in the caliber of the glands, the typical "Swiss cheese" pattern characteristic of hyperplasia being present (Fig. 1). The epithelium lining the glands was for the most part higher than that

lining normal glands. There was no appreciable change in the stroma. There was considerable invasion of the myometrium by the glands and stroma of the endometrium. Several small fibroid nodules with considerable hyaline change were in the uterine wall. Both tubes were normal. The left ovary was a normal senile structure showing the usual histologic changes incident to advanced age. The right ovarian tumor was composed partially of solid tumor tissue and partially of cysts varying from minute size to 3 cm. in diameter. The cysts were follicle-like structures, the minute ones suggesting primordial follicle, the larger ones the more mature follicle, and the largest ones resembling graafian follicle cysts (Fig. 2). The content of the follicular spaces was a homogeneous eosin-staining substance. Mixed with this substance in certain of the cysts were blood and cellular débris (Fig. 3). The cysts were lined with a zone of cells closely resembling the granulosal cells of a normal follicle. Between these cystic structures were solid areas of these cells, in some areas closely packed, while in other areas columns and clusters of the

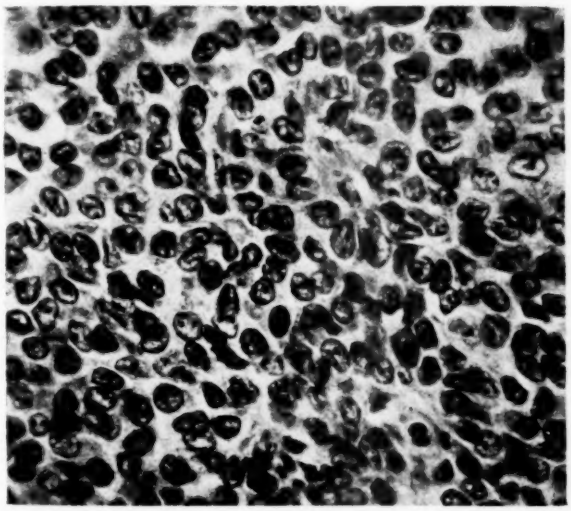

Fig. 4.—High power field of the tumor cells of Case 1. Note their uniform character.

cells were separated from one another by fibrous tissue. Examination of the tumor cells under higher magnification showed them to be very uniform in size and shape (Fig. 4). An occasional mitotic figure was seen. The tumor was very vascular.

Pathologic Diagnosis.—Granulosal cell tumor of the right ovary; hyperplasia of the endometrium; adenomyoma of uterus; small intramural fibroids.

Case 2.—Mrs. E. T., aged fifty, complained of enlargement of the abdomen and vaginal bleeding. The menstrual history had been normal up to the menopause, which had occurred eight years previously. She had had seven full-term pregnancies and one seven months' premature child. Four years after the cessation of her menses she again began to bleed irregularly. The interval was one to three weeks, the duration four to five days. At times the bleeding was scanty, at times profuse. Two years before she came to us she had first noticed enlargement of her abdomen, which had steadily increased in size. Two months previous to admission the cervix had begun to protrude from the vagina.

General examination showed a poorly nourished woman, moderately anemic (hb. 70 per cent). The abdomen was markedly enlarged, palpation and percussion suggesting the presence of a huge abdominal tumor. Pelvic examination showed the

cervix protruding from the outlet. It was not ulcerated. The entire pelvis was choked with a huge cystic mass extending up to the xiphoid. The uterus could not be outlined.

Operation.—Through a long midline incision, the huge right-sided ovarian tumor, which was perfectly free in the abdomen, was removed. The uterus was flattened

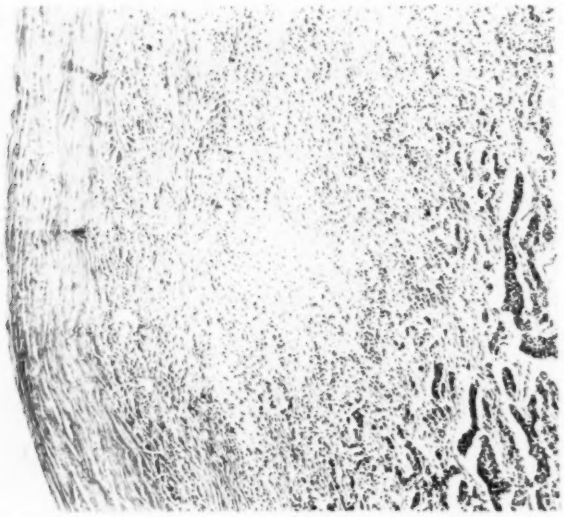

Fig. 5.—Section from periphery of tumor of Case 2. Note the heavy fibrous capsule.

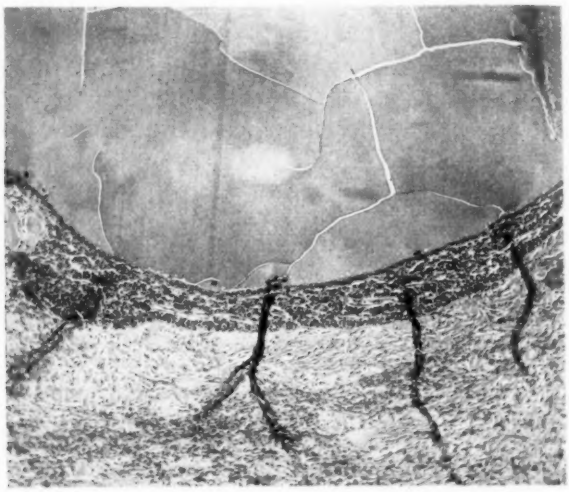

Fig. 6.—Portion of wall of large cystic follicular structure from Case 3.

out as a result of the pressure of the cyst. The left ovary appeared normal. Because the patient's condition would not warrant further operation, the uterus was fixed to the abdominal wall and the abdomen closed.

The patient made an uneventful recovery and is well two years after operation.

Pathology.—Gross: The tumor consisted of a large, soft, apparently cystic structure, 30 cm. in diameter and weighing 20¼ pounds. It was smooth externally and

free from adhesions. The elongated tube was attached to it. On section the tumor was multilocular, the loculcs varying in diameter from several centimeters to one or two millimeters. The loculcs were lined by a smooth surface and filled with a slightly viscid, straw-colored fluid. The walls between the loculcs varied in thickness from a millimeter to two or three centimeters, and varied in color from yellow to a flesh pink. Nowhere was there any evidence of papillary growth.

Microscopic: The tumor was completely enclosed by a heavy fibrous capsule (Fig. 5). The cysts were lined with a zone of columnar and polygonal cells with dark-blue staining nuclei resembling normal granulosal cells (Fig. 6). Within this zone of cells there was in many of the cysts an inner zone of hyalinized fibrous tissue. This was true in most of the larger cysts, whereas the smaller ones were lined directly by the granulosa-like cells. Between these follicle-like structures was a fibrous stroma invaded markedly by tumor cells which also were of the general character of granulosal cells. The cells were generally uniform in size and shape and no mitotic figures were seen. The fibrous stroma showed extreme hyalinization.

Pathologic Diagnosis.—Granulosal-cell tumor of ovary.

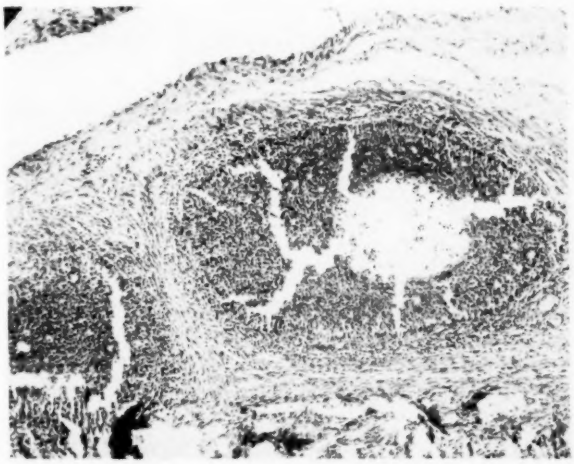

Fig. 7.—Small tumor from Case 3. It is composed of two portions, the follicular structure shown above and a solid portion, part of which is shown in the lower part of the photomicrograph. Note the lightly staining cells about the periphery of the follicle, resembling theca interna cells.

Case 3.—Mrs. R. M., aged 43, complained of vaginal bleeding. The menstrual history up to the present illness had been quite normal. During the past year the menses had gradually increased in profuseness and in duration until the past month, when bleeding had been constant. She now complained of weakness and shortness of breath.

Examination revealed a well-nourished, extremely anemic woman. Hemoglobin only 17 per cent. Pelvic examination showed that the vagina was completely filled with a pedunculated fibroid attached to a pedicle which passed up into the uterine cavity through the dilated cervix. The uterus was transformed into a multinodular fibroid. After one transfusion of 600 c.c. of blood a vaginal myomectomy was done. A second transfusion of 550 c.c. of blood was given.

Operation.—Hysteromyomectomy, double salpingo-oöphorectomy.

Pathology.—Gross: The uterus was enlarged and distorted by the presence of several intramural fibroids. The endometrium was smooth and rather thin. Both tubes were small, thin-walled structures but covered with shaggy adhesions. Both ovaries were of normal size but each was adherent to its corresponding tube.

Microscopic: The fibroids showed the usual microscopic picture. The endometrium showed the postmenstrual pattern but otherwise was not noteworthy. The tubes showed moderate fibrous and round-cell infiltration. The left ovary showed several corpora albicantia but no corpora lutea or follicles. In the medulla of the ovary, near the hilum, was a tumor, about 3 mm. in diameter. It was composed of two parts, the one follicular in contour and the other a solid mass of cells of the same nature as those forming the follicular structure (Fig. 7). The follicular structure was composed of granulosal-like cells arranged about a central cavity containing some eosin-staining homogeneous material and red blood cells. The cells at the periphery of the zone of granulosal cells were columnar in type, while the others surrounding the central cavity were closely packed polygonal cells. Surrounding this structure was a zone of lightly staining cells closely resembling normal theca interna cells (Fig. 7). The solid portion of the tumor was composed of cells of exactly the same type. Scattered through the whole tumor were small vacules immediately surrounded by cuboidal cells. Mitotic figures were frequent but most of the cells were very uniform in size and staining qualities.

Pathologic Diagnosis.—Myomata uteri; chronic salpingitis; very early granulosal-cell tumor of right ovary.

Morphology.—Granulosal-cell tumors of the ovary are for the most part unilateral, although occasionally a bilateral growth is described. In the majority of the cases, the tumor occurs alone without any other pathologic condition of the ovary, but Meyer described a granulosal-cell tumor and fibroma in combination, as well as one associated with a papillary cystoma. In size they usually vary from the almost microscopic tumor, discovered accidentally, to the size of a man's head. In many cases described, the tumors are hardly larger than a normal ovary. Our Case 3 illustrates one of the smallest tumors, being about 3 mm. in diameter, while our Case 2 is an outstanding exception, the tumor being 30 cm. in diameter and larger than any I have found described in the literature. The tumors are, for the most part, very well encapsulated by a thick fibrous capsule (Fig. 5). As a result of their semicystic structure they are usually soft and spongy in consistence. This is particularly true of the larger tumors in which cyst-like structures attain a considerable diameter. On section the growths reveal their semicystic nature. The more solid portions of the tumor contain small round spaces just within the range of visibility. Other parts of the tumor contain cysts several centimeters in diameter, the content of which is a clear straw-colored fluid. Considerable blood also pours forth on section, indicating marked vascularity. The cut surface is fleshy in color.

Microscopically the neoplasms are characterized by two features: (1) the resemblance of the tumor cells to granulosal-cells of the normal ovary; (2) the tendency to form structures resembling graafian follicles and follicular cysts. Meyer describes two histologic types, the folliculoid and cylindroid. In the former the follicular structure dominates, whereas the latter is a solid structure composed of these same granulosal cells broken up into strands and figures to form

bizarre patterns by the ingrowth of connective tissue stroma (Fig. 8). Both of the structural types are usually present in variable proportions in the same tumor, although tumors are described of practically the pure folliculoid and of the pure cylindroid type. The smallest follicles are lined with a single layer of cuboidal or flattened epithelial cells and in size approximating the normal primordial follicles. The larger folliculoid structures are bounded by a zone of closely packed polygonal cells with dark-blue staining nuclei and scanty cytoplasm. Limiting this zone of cells at its periphery there is frequently a hyalinized basement membrane. The first layer of cells adjacent to this basement membrane is cuboidal. Within the zone of granulosa-like

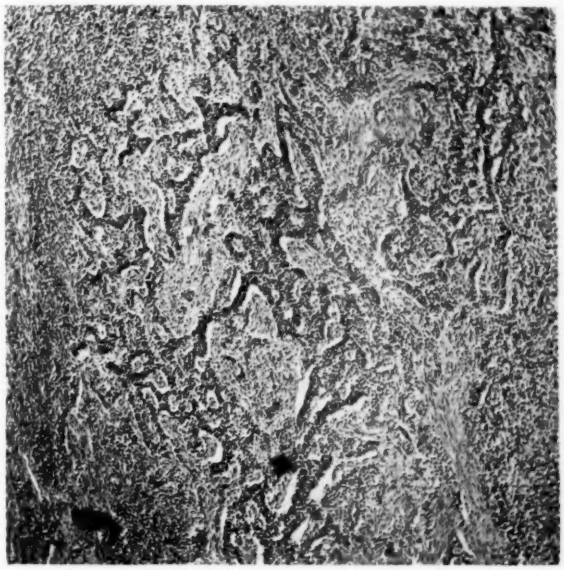

Fig. 8.—Solid portion of tumor of Case 2. The tumor cells are broken up into strands by fibrous stroma, forming the so-called cylindroid type of granulosal tumor.

cells, separating it from the central cavity, there is frequently an inner zone of hyalinized fibrous tissue of variable width (Fig. 9). This is particularly true in the larger cysts, whereas it is uniformly absent in the small structures resembling the primordial follicles. Very rarely a band of clear lightly staining cells surrounds the zone of granulosa-like cells, resembling the theca interna cells of a normal follicle (Fig. 7). The content of these folliculoid structures is an eosin-staining homogeneous substance, often containing a small amount of blood and cellular débris. In spite of a careful search no cells resembling ova were found in these follicular structures. The tumors are, for the most part, quite vascular. Blood vessels of various sizes are numerous, and frequently large blood spaces are seen, lined with a single layer of very flat epithelium (Fig. 10).

Under the high power magnification the low columnar and polygonal tumor cells are very uniform in size, shape and staining qualities (Fig. 4). The light eosin-staining cytoplasm, for the most part, is scanty. The nuclei are round or oval and take a rather deep hematoxylin stain. In the very small tumor of Case 3 mitotic figures are moderately frequent. In the moderate-sized tumor of Case 1 mitotic figures are occasionally seen, but in the huge tumor of Case 3 no mitoses are seen. In this, the largest and probably the oldest tumor of our series, there is a much greater proportion of fibrous stroma and extreme hyalinization. The presence of mitoses in the smaller tumors, their absence in the largest one, and the extreme fibrosis and hyalinization of the huge tumor, would seem to indicate that the younger

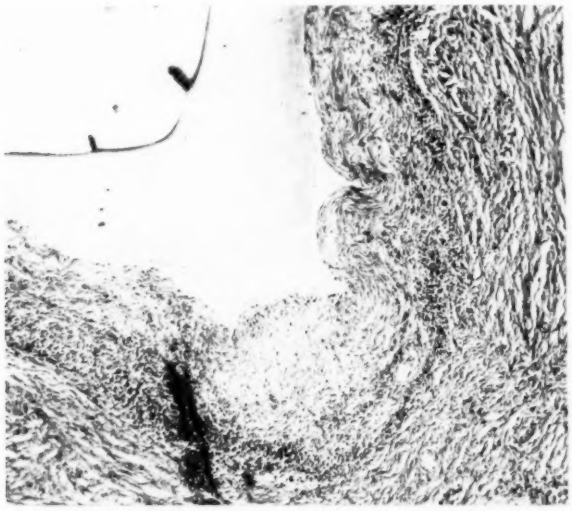

Fig. 9.—Section of wall of large follicular structure from Case 2. Note the heavy fibrous zone separating the poorly preserved granulosal layer from the cavity.

the tumor the more active the growth, whereas the largest and oldest tumor shows very little evidence of active growth and marked evidence of fibrosis and degeneration.

Histogenesis.—There are several characteristics of these tumors which would seem to suggest their origin from granulosal epithelium. The histologic character of the tumor cells, the tendency to form follicle-like structures, and the apparent effect of the tumor upon the endometrium in the formation of hyperplasia, all suggest that the tumor cells are related to granulosal cells. Concerning the exact origin, two possibilities present themselves. One of these is that the tumors arise from the adult granulosal cells of the graafian follicles and the other, that they arise from embryonic rests of ovarian parenchyma, which genetically is closely related to the adult granulosal cells. In order to understand better the histogenesis of these tumors

it might be well to review briefly the embryologic development of the ovary. The organ arises, as does the testis, as an indifferent sex gland on the ventro-mesial surface of the urogenital fold. The celomic epithelium in this region becomes several layers thick, the mass of cells thus formed lying adjacent to the mesonephros. Soon the epithelial mass becomes differentiated into a layer of superficial surface epithelium and an inner cell-mass. From this inner cell-mass arise the ova cells, the granulosal cells, the medullary cords and the rete ovarii. The ovarian stroma is developed by an ingrowth of connective tissue from the adjacent mesonephros. Beginning with the third month some of the epithelial cells of the medulla and cortex degenerate to allow the ingrowth of this stroma. By virtue of this ingrowth of connective tissue the epithelial cells are separated into clusters, the so-called

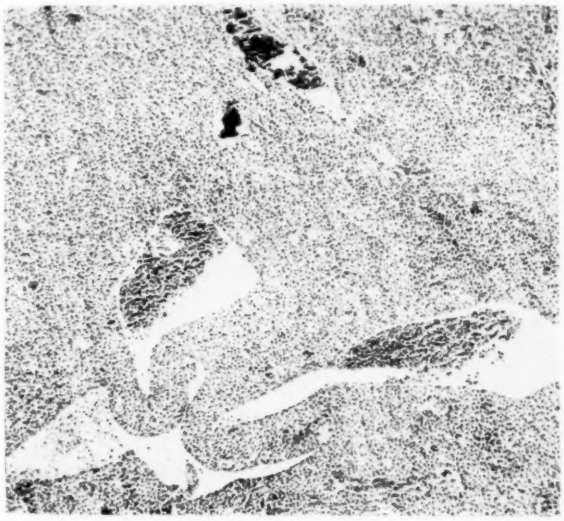

Fig. 10.—Field from solid portion of tumor of Case 1. Note the large thin-walled blood spaces.

egg-nests, containing the cells destined to become ova and their surrounding flattened epithelium, the early granulosa cells. Early in the development of the ovary a medullary and cortical portion can be recognized. In the medullary portion the parenchyma forms medullary cords and rudimentary follicles which soon degenerate. The primordial follicles in the cortex persist so that at birth and thereafter the follicles are limited to the cortex.

Robert Meyer has favored the view that the tumor cells originate from the embryonal parenchyma rests. He believes that the origin of a tumor from the adult granulosal cells is very unlikely because the growth of those cells depends so absolutely upon the life of the ovum. Under no condition, such as in inflammations, has he ever observed any proliferative tendency on the part of the follicular epithelium.

The active proliferation of the granulosal cells into lutein cells begins at the death of the ovum. The majority of these tumors occur after the menopause when the ova have been absent for some years. Upon the basis of this slave-like subordination of adult granulosal cells to the living ovum, Meyer feels that neoplastic activity of these adult cells is very unlikely. This evidence, however, is chiefly against the origin from mature follicles rather than positive evidence in favor of their origin from embryonal rests.

Our Case 3 shows an extremely early but completely formed granulosal-cell tumor discovered accidentally in routine section of the ovary. It is situated in the medulla near the hilum of the ovary. Our knowledge of ovarian histology teaches us that in adult life the follicles are limited to the ovarian cortex. The origin of this very early granulosal tumor in the medulla practically excludes an adult follicle as its origin. In the medulla, as above described, there is much ovarian

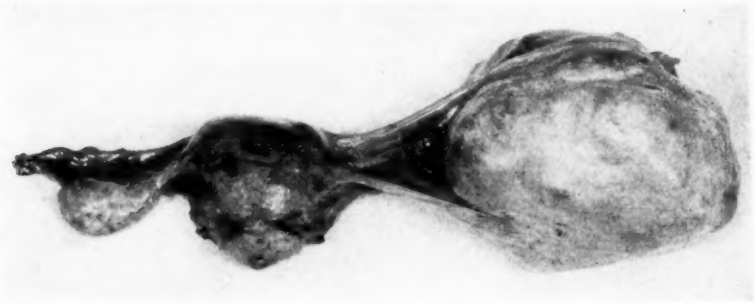

Fig. 11.—Gross specimen from Case 4. Note the well encapsulated tumor which was about the size of a grapefruit, and the uterus, which was as large as that of a woman during active menstrual life.

parenchyma in embryonic life which degenerates more or less completely before birth. By virtue of the position of this small tumor it would seem that embryonal rests of this epithelium, very closely related to the adult granulosal epithelium, would be practically the only possible origin of this granulosal tumor in the ovarian medulla. Therefore in our Case 3 I feel that its origin from embryonal granulosal rests is clearly indicated. Further observations on extremely early tumors would be of great value in establishing still further the histogenesis of these neoplasms.

The following is a case illustrating a tumor similar to that described by Brenner as oöphoroma folliculare. The history of profuse recurrent postmenopausal bleeding, as well as the tendency to form follicular structures, suggests a relationship to the granulosal-cell tumors, but the individual cells do not closely resemble the granulosal-cells of the above tumors. Because of this probable relation to the granulosal-cell tumors it is reported:

CASE 4.—Mrs. G. H., aged sixty-two, complained that her menses had never ceased. On close questioning, however, it was learned that her periods had been quite regular until eight years previously. She then had amenorrhea for six months. Since that time she had bled irregularly, each bleeding being fully as profuse as a normal menstrual period. Never was there a period free from bleeding of more than a month, the interval usually being considerably less than thirty days. She had been married thirty-five years and had had five full-term pregnancies and two early, spontaneous abortions. For the past three months bleeding had been almost constant and at times very profuse. Hemoglobin 75 per cent.

General examination showed a large, raw-boned woman, 6 feet, 1 inch tall and weighing 215 pounds. She had marked hypertrichosis of the face, having shaved daily for years. For the past few years she had been known to have diabetes mellitus and was using insulin daily.

Pelvic examination showed the cervix transversely lacerated, but otherwise normal. The body of the uterus was rather large for the patient's age and in anteposition.

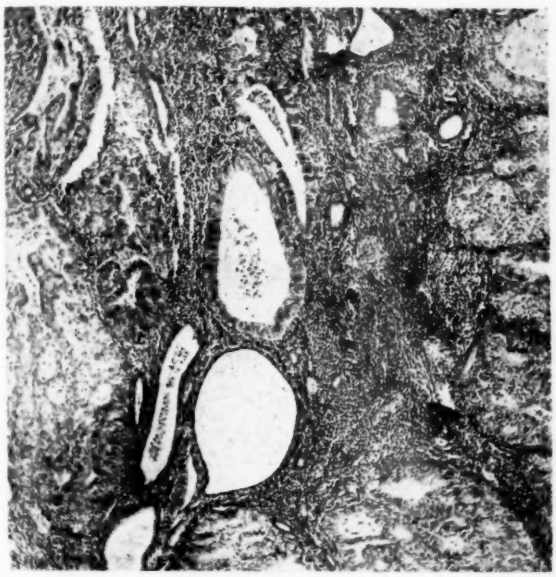

Fig. 12.—Section of endometrium from Case 4. Within the carcinomatous areas as benign endometrial glands showing the hyperplasia pattern.

Behind the uterus was a very firm, nodular tumor, the size of a grapefruit, occupying the culdesac and extending to the lateral pelvic walls.

Operation.—Supravaginal hysterectomy; double salpingo-oöphorectomy.

The patient had a pulmonary infarct 17 days after operation, which she survived and is well one year later. She was given radium in the cervical stump because of the discovery of carcinoma of the endometrium.

Pathology.—Gross: The specimen consisted of a uterus considerably larger than normal for the patient's age, a small, senile left ovary, a normal-appearing left tube, and a tumor 14 × 11 × 8 cm. which replaced the right ovary, across which the right tube was stretched (Fig. 11). Upon sectioning the uterus, the endometrium was seen to be greatly thickened and roughened down to a point about 3 mm. above the point of amputation. Its gross appearance suggested carcinoma rather than hyperplasia. The right ovarian tumor was a grossly nodular, encapsulated, very firm tumor, yellowish white in color. The external fibrous capsule was smooth and

glistening, there having been apparently no adhesions between it and the surrounding structures. On section, the tumor appeared much like the usual fibroma, but on close inspection innumerable small cavities from pinhead to pinpoint size could be seen, filled with a yellowish gelatinous material (after fixation).

Microscopic: Most of the endometrium was transformed into a typical adenocarcinomatous growth which had invaded the myometrium very slightly. Between the carcinoma, small areas of nonmalignant endometrium were seen. These nonmalignant glands were extremely variable as to caliber and suggested hyperplasia of the endometrium (Fig. 12).

The left ovary showed the usual histologic picture of a senile ovary.

The right ovarian tumor was enclosed in a thick fibrous capsule. The stroma of the tumor was very abundant, composed of closely packed spindle-shaped cells resembling normal ovarian stroma. Invading this stroma were islands of epithelium, some solid and others arranged about a central cavity containing eosin-staining

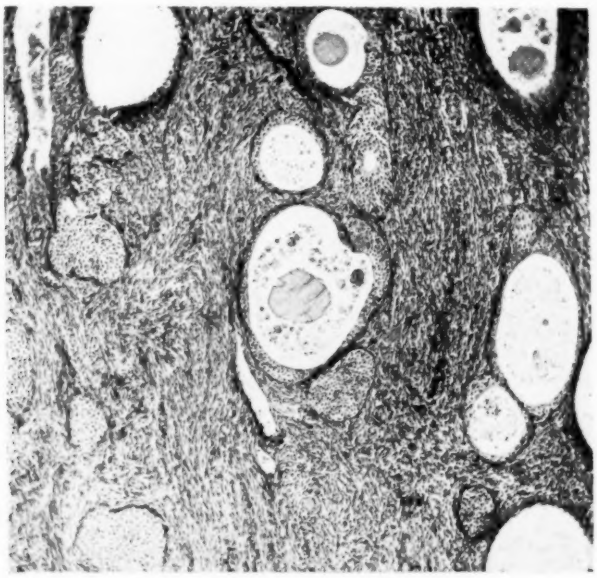

Fig. 13.—Section of ovarian tumor of Case 4. Note the follicle-like structures and the islands of solid tumor cells between which is an abundant fibrous stroma.

homogeneous substance and cellular débris (Fig. 13). In some of the follicular structures the surrounding epithelium was completely degenerated, leaving simply a cavity within the fibrous stroma. The tumor cells were oval or polygonal in shape with round or oval vesicular nuclei. There were no hyperchromatic nuclei and no mitoses.

Clinical Considerations.—Considering a neoplasm from a clinical point of view, perhaps the most important question concerns its malignancy. From a purely structural standpoint this group occupies rather a middle position. All of our four tumors were very well encapsulated. Even the huge 30 cm. granulosal tumor, which had a history of at least four years' duration, was perfectly encapsulated and lay free in the abdominal cavity. The tumor cells of our granulosal-cell tumors, as well as the oöphoroma folliculare invaded the fibrous

stroma of the tumor much in the manner of a malignant growth, but there is no invasion of the fibrous capsule. The tumor cells are, for the most part, very uniform in size and staining qualities. Mitoses, however, were frequently seen in the extremely small tumor but were entirely absent in the largest tumor, and a great deal of fibrosis and hyalinization were present. This suggests that perhaps in the very early stage growth is quite rapid but eventually, with fibrous tissue proliferation and diminution in the blood supply, growth becomes impaired and hyalinization results. Our case of oöphoroma folliculare also had a great abundance of fibrous stroma surrounding the various follicle-like structures.

However valuable histologic study may be in predicting the nature of a given tumor, the final criterion of malignancy is whether or not the tumor is capable of causing the death of the patient. To determine this, a search was made in the literature for end-results. Unfortunately, many of these tumors are reported from the pathologic rather than the clinical point of view, and end-results are not available. Brenner considered his cases of oöphoroma folliculare as benign. In one of his cases the tumor had been kept under observation for four years prior to operation and surgical measures were undertaken only when an increase in size could be detected. At operation no evidence of extension of the tumor was made out. The patient died eight days after operation of intestinal obstruction. The history of our case prompts me to agree with Brenner as to the benign nature of these tumors, for in spite of a history of eight years' duration the tumor was perfectly free in the pelvis and the patient is well a year after operation. It will be seen by reference to Table I that the granulosal-cell tumors have been labelled carcinoma by various authors. It will be noted, however, that in many of the cases there has been no follow-up and that the label of malignancy has been made entirely on histologic grounds. Only four of the cases have been followed until death. One of these, Neumann's patient, died six days after operation. In this case, however, there was an associated malignant papilloma. Hence, this death cannot be fairly attributed to the granulosal tumor. In Aschner's Neumann's and Voigt's cases all the patients died six months after operation, with definite recurrences. On the other hand, in this small series of 33 cases, only 17 of which were followed, 13 of the patients are reported as well from one to eleven years after operation. From these data we have concluded that the majority of the tumors are relatively benign but that malignant forms occasionally occur. Certainly, the majority of the tumors are sufficiently benign to insure an excellent chance of operative cure.

Reference to Table I will show that, although cases are reported in young women, the majority of these tumors occur after the cessation of the menses. The average age in this small series from the literature

TABLE I. SHOWING AGE INCIDENCE AND ULTIMATE FATE OF PATIENTS

AUTHOR	NAME APPLIED TO TUMOR	AGE	END-RESULT
Aschner	1. Granulosal-cell tumor	Near menopause	Died 6 months after operation with recurrence
	2. Granulosal-cell tumor	25	Well 1½ years after operation
Blau, A.	Carcinoma of ovary (Follicular-like structure)	33	Not given
Brenner	1. Oöphoroma folliculare	62	Died 8 days after operation—intestinal obstruction
	2. Oöphoroma folliculare	"Old woman"	Incidental finding at autopsy
	3. Oöphoroma folliculare	72	Incidental finding at autopsy
Gloekner	Cylindroma	50	Not given
Gottschalk	Folliculoma ovarii malignum	48	Well 4½ years after operation
Isbruch	1. Granulosal-cell tumor (Carcinoma cylindromatosum)	60	Well 11 years after operation
	2. Granulosal-cell tumor (Carcinoma cylindromatosum)	70	Well "some time" after operation
King, E. S. J.	1. Granulosal-cell tumor	51	Not given
	2. Granulosal-cell tumor	62	Not given
Krompecher	1. Follicular oöphoroma	60	Not given
	2. Follicular oöphoroma	?	Not given
Meyer	1. Fibroma and granulosal-cell tumor	53	Not given
	2. Dermoid and cylindroma	70	Not given
	3. Granulosal-cell (cylindroid)	60	Not given
	4. Carcinoma folliculoides	63	Not given
Müllerheim	1. Granulosal-cell tumor (malignant)	72	Not given
	2. Granulosal-cell tumor	69	Well 8 years after operation
Neumann	1. Carcinoma folliculoides	50	Died 6 months after operation with recurrence. Metastasis found in gland at operation
	2. Ovarian carcinoma with cylindroid structure	34	Well 2½ years after operation
	3. Granulosal-cell tumor	36	Well 2½ years after operation
	4. Carcinoma cylindromatosum	35	Well 2½ years after operation
	5. Medullary carcinoma with follicular cysts	16	Well 2½ years after operation
	6. Fibroma, Malignant papilloma, Carcinoma cylindromatosum	61	Died 6 days after operation
Robinson	Folliculoid carcinoma	59	Not given
Scheyer	Granulosal-cell carcinoma	40	Not given
Schröder	Granulosal-cell tumor	45	Not given
Te Linde	1. Granulosal-cell tumor	65	Well 4 years after operation
	2. Granulosal-cell tumor	50	Well 2 years after operation
	3. Granulosal-cell tumor	43	Well 2 years after operation
	4. Oöphoroma folliculare	63	Well 1 year after operation
Tietze	Granulosal-cell tumor	35	Not given
Voigt	Carcinoma folliculoides ovarii	47	Patient died in 6 months of recurrence
v. Kahlden	Adenoma of graafian follicle with transition to carcinoma	Young girl	Not given

is fifty-two, the oldest patient being seventy-two and the youngest sixteen. In 70 per cent the tumors occurred after the age of forty-five. In the cases occurring during the menstrual life practically all the women had some disturbance of menstrual function, usually metrorrhagia. In our Case 1, twenty-two years after the onset of the menopause, the patient began to bleed approximately every month for a few days, over a period of six months. In Case 2 the patient began to bleed irregularly four years after the cessation of her normal menstrual life. In Case 4 the sixty-three year old patient stated that she had never stopped menstruating. Close questioning, however, brought out the fact that eight years before, at the age of fifty-five, she had not menstruated for a period of six months. This may probably be interpreted as the normal menopause, the recurrence of bleeding being due to the presence of ovarian tumor. The profuse bleeding, three months before the operation, was undoubtedly explained on the basis of carcinoma of the endometrium. These histories of postmenopausal bleeding are typical of those reported in the literature with this type of tumor. The question naturally arises whether the granulosal-cell tumors and the closely related oöphoroma folliculare are the only ovarian tumors associated with bleeding after the menopause. A survey of the literature, as well as of our own ovarian tumors occurring at this time of life, brings out the fact that bleeding may occur with other ovarian tumors. Schiffmann, who has been particularly interested in ovarian tumors associated with postmenopausal bleeding, has reported several types of ovarian carcinoma occurring in old women with vaginal bleeding. Moulonguet-Doleris found bleeding in 19 of 74 cases of various types of benign and malignant ovarian tumors after the menopause. Robert Meyer reported a round-cell sarcoma and fibroma of the ovary associated with postmenopausal bleeding. Scheyer collected from the literature seven cases of ovarian carcinoma and two cases of ovarian sarcoma following the artificial menopause produced by radium therapy. In the gynecologic-pathologic laboratory at Johns Hopkins Hospital we have had, in the past ten years, 41 cases of tumor of the ovary from postclimacteric women. In 9 of these 41 cases there was vaginal bleeding. In 3 of the 9 cases this bleeding could be readily explained on the basis of the extension of the carcinoma of the ovary to the uterus or vagina. In two others, which were diagnosed inoperable carcinoma of the ovary at operation, there was probable extension to the uterus, but as the specimen was not removed this could not be proved. Of the remaining 4 cases with bleeding, 1 was a fibroma, 1 an adenocarcinoma and 2 cystadenomas. In none of these cases, however, was there profuse recurring periods of bleeding associated with the tumors of this special group.

In Cases 1 and 4 the uteri were removed and were available for study. In Case 2 the uterus was not removed nor was special mention

made of it in the operative note. In Case 3 the uterus was a multiple fibroid structure and the small ovarian tumor only an accidental finding on section of the ovary. In Cases 1 and 4 the uteri, instead of being the usual senile structures of women long past the menopause, were the size of normal uteri of women in years of active menstrual life, notwithstanding the fact that the patients were sixty-five and sixty-three years of age. This unusual size of the uterus is mentioned by several authors who have reported tumors of this group. The endometria in both of these cases were remarkable. They showed no evidence of senile change compatible with the ages of the patients. In Case 1 the endometrium showed marked hyperplasia (Fig. 1). In Case 4 most of the endometrium was involved in the carcinomatous growth. Between the carcinomatous areas, however, were areas of dilated nonmalignant glands, suggesting that hyperplasia had preceded the carcinoma (Fig. 12). The history of bleeding for eight years is compatible with this view, for certainly the carcinoma which had not yet invaded the myometrium was not responsible for bleeding over so long a period. Rather may it be assumed that the hyperplastic endometrium was responsible for the bleeding except for the recent continuous, profuse bleeding of the last three months which was undoubtedly chiefly due to the carcinoma. In Case 3 the endometrium showed no evidence of hyperplasia, a fact which is not surprising when one considers the minute size of the granulosal tumor. Whether hyperplasia of the endometrium always accompanies a well-developed tumor of this group we are not prepared to say, but it certainly is a frequent finding. In several cases in the literature the fact that hyperplasia of the endometrium is present is definitely stated. In the other cases, in almost every instance, the statement is made that the endometrium is "thickened," "hypertrophied," "polypoid," or "shaggy," descriptive terms which suggest very strongly hyperplasia. The frequent presence of hyperplasia of the endometrium accompanying these tumors is very suggestive that there is some causal relation between the tumors and the condition of the endometrium, and that bleeding results by virtue of the hyperplastic endometrium. According to our present conception of the pathologic condition known as hyperplasia of the endometrium, it is a disease occurring during the menstrual life of a woman dependent upon pathologic ovarian function. Both Meyer and Schröder, working independently, concluded that it was due to a persistence of follicular influence and an absence of corpus luteum influence. They based this conclusion on considerable pathologic material in which a careful search failed to show any corpora lutea in the ovaries but frequent follicles and follicular cysts. If this theory is correct, its occurrence naturally would be limited to the years in which follicles are present in the ovary, that is, before the menopause. An occasional case is reported within several months

after the final menstruation. This is compatible with the above mentioned theory for, just as a woman undergoing the menopause may menstruate six months or a year after her previous menstruation as the result of the development and final retrogression of a last corpus luteum, so a follicle developing and persisting several months after the last menstruation might be responsible for the development of hyperplasia of the endometrium. So apparently in the case of these tumors occurring many years after the menopause this hyperplastic condition of the endometrium may be produced by a pathologic follicular influence due to the development and growth of a neoplasm resembling in form an aggregation of follicles. Certainly this endometrial condition, as well as the large size of the uteri in old women, speaks for some hormonal influence of the tumor and strengthens the view that their origin is from cells which are, at least genetically, related to the normal granulosal cells.

From the above clinical and pathologic study, certain facts are obtained which may be of distinct value in dealing with postmenopausal bleeding. Everyone has had the experience, in investigating the underlying pathology of this symptom, of being at a loss occasionally to explain satisfactorily the bleeding after carrying out the usual diagnostic procedures. The fact that malignancy somewhere in the genital tract is so frequently responsible for the symptom makes it imperative that every effort should be made to discover the underlying lesion. We have shown above that bleeding may occur with other benign and malignant ovarian tumors as well as with the tumors of follicular structure. Should curettage of the uterus reveal a normal endometrium, the possibility of an ovarian tumor, too small to cause palpable ovarian enlargement, should be considered and the patient kept under close observation. Schiffmann has particularly stressed this point. His opinion has been influenced by several cases coming under his observation in which bimanual examination showed no ovarian enlargement and curettage of the uterus showed a normal endometrium at the time the patient presented herself complaining of bleeding. Subsequently these patients have returned with inoperable ovarian carcinomata which doubtless were present at the time of the original examination, but were too small for detection bimanually. Should curettage, done for postmenopausal bleeding, disclose hyperplasia of the endometrium, the possibility of an ovarian tumor of the folliculoid group should be borne in mind. If bimanual examination fails to detect ovarian enlargement the patient should be kept under observation and as soon as ovarian enlargement is noted should be subjected to a laparotomy, provided there is no contraindication to operation in her general medical condition. This is particularly important because the follow-up of the cases cited above has shown that operation offers an excellent chance for cure in these tumors.

SUMMARY

Three cases of granulosal-cell tumor of the ovary and one of the closely related oöphoroma folliculare have been reported and described histologically. The histogenesis of granulosal-cell tumors has been discussed. Evidence has been produced in the form of an extremely early tumor which would indicate that the probable origin is from embryonic rests of ovarian parenchyma in the medullary portion of the ovary. Clinically, the tumors occur most frequently after the cessation of the menses and are usually associated with bleeding. The importance of early diagnosis and operation has been emphasized, particularly because the tumors are sufficiently benign to offer an excellent chance of surgical cure.

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THE EARLY DIAGNOSIS OF ADNEXAL CANCER

By Brooke M. Anspach, M.D., Philadelphia, Pa.

INCIDENCE

ALTHOUGH cancer of the adnexa is much less frequent than cancer of the uterus it occurs sufficiently often to make it a menace.

Primary cancer of the tube is rare. About 232 cases are on record. It occurred once in 19,439 patients in the Gynecological Service at the University Hospital, Philadelphia (statistics furnished through the courtesy of Dr. C. C. Norris), three times in 30,000 cases at the Bellevue Hospital in New York; five times in 35,000 cases at the Johns Hopkins Hospital in Baltimore; once in 3,844 cases admitted to the Gynecological Service at the Jefferson Hospital since September, 1922. Stübler and Brandess list it as forming 0.45 per cent of all genital cancers, the same rating they give for cancer of the clitoris. Although it appears very rare yet the menace of it is emphasized by the fact that Wharton and Krock reported a series of 14 cases, 5 of which occurred in the Johns Hopkins Hospital, the remainder in neighboring hospitals and all but two in the hands of members of their own staff. In private practice I have had two cases within the past two years.

Cancer of the ovary is much more common. The incidence as given in reports varies considerably, thus at the University Hospital 26 per cent of all ovarian newgrowths were malignant. At the Jefferson Hospital 23 per cent were of that description. Stübler and Brandess' proportion was 28 per cent and Zweifel and Döderlein each had about 10 per cent. Stübler and Brandess note the relative frequency of location in genital carcinoma as follows: cervix, 61.27 per cent; body, 16.04 per cent; ovary, 16.85 per cent; vulva, 2.9 per cent; vagina, 1.97 per cent; tube, 0.45 per cent; clitoris, 0.45 per cent.

Byron and Berkoff note the relative frequency of carcinoma of the uterus and of the ovary as follows: cancer of the cervix, 1.8 per cent; cancer of the body, 0.99 per cent; cancer of the ovary, 0.27 per cent.

Our own statistics at the Jefferson Hospital are as follows: 3,844 patients admitted from September, 1921, to January 1, 1930. Cancer of the cervix occurred in 179, 4.65 per cent; cancer of the body in 37, 0.96 per cent; cancer of the ovary in 26, sarcoma of the ovary in 2, a total of 28, 0.70 per cent.

PROGNOSIS

The prognosis of adnexal cancer is bad. The actual percentage of recovery in the patients on record with primary cancer of the tube

is difficult to estimate but with operation and x-ray combined it is probably not more than 4 per cent.

The prospect for patients with cancer of the ovary is much more favorable, but the percentage of five-year cures is decidedly less than in cancer of the uterus.

Nearly all cases of primary cancer of the tube reach the surgeon in an inoperable stage and the same is true in about half the cases of cancer of the ovary.

Adnexal cancer in the early stage for the most part is revealed by accident, during the course of pelvic operations for other purposes or upon examination of pelvic specimens supposed to be benign. For a reasonable chance of curability adnexal cancer must be found at an earlier stage, because it is so rapidly disseminated; being intraperitoneal to begin with, it is likely that particles of the growth are quickly set free among the neighboring coils of intestine; whether this occurs or not the encapsulating action of the omentum and the vascular drainage from the pelvis toward the diaphragm at a very early stage spreads the disease beyond its primary location.

The follow-up statistics in the reported cases of cancer of the tube are meager. In Wechsler's tabulation of 192 cases he says that only 6 were reported as having had no recurrence three or four years following operation. Wharton and Krock in 14 cases had one 3, one 4 and 5-year cure. The last mentioned patient died five years after the operation apparently from intercurrent illness. Schlaak in 1925 reported that there were only two five-year cures on record. The author's first case died within eight months of the operation and the second one, an early cancer with an excellent chance for a permanent cure, died within a week of the operation. Perhaps the estimate of Beck that the permanent cures from operation and x-ray combined is 4 per cent closely approximates the truth. It is very evident from a study of the details of the reported cases that the poor results have come from late recognition of the disease.

The prognosis in cases of cancer of the ovary is much better. Thus Byron and Berkoff report 79 operations, 53 patients traced, 12 alive, average of 4 years and six months to nine years after operation. Zweifel and Payr report 72 operations, 10 of the patients alive, six for more than five years. Schleyer reports 81 operations, 12 living and well of five-year cases. Norris reports 86 operations, 56 patients traced, 21 alive for three or more years. Stübler and Brandess had 122 operations; 30 are alive and free of recurrence at the end of three years.

Our own results at the Jefferson Hospital have to do with 28 cases, 26 carcinoma, 2 sarcoma. Of these one is untraced; 14 are dead (3 postoperative); 5 are living and symptom-free for less than three years; 5 are living and ailing (repeated x-ray treatment) 18 months and 6 months; 6 are ailing and symptom-free, two for three years, two for four years, one for seven, one for eight years. It should be noted that two of the cases living for more than three years were sarcoma of the ovary—round cell and spindle cell—and curiously enough in each case the attention of the patient was drawn to her condition by the acute pain occasioned by a twist of the pedicle. Although strictly speaking they are not cancers of the ovary their clinical significance is identical. I have two other cases in my series of 115 ovarian cysts which are not listed as malignant. Gross and histologic examination of the tumors after operation failed to show malignancy, yet both died later of a general carcinomatosis of the abdominal cavity. In the first the

symptoms developed so soon after the operation that I am convinced an area of carcinomatous degeneration in the tumor was overlooked. The second patient was stricken rather suddenly about two and a half years after the operation. Although it is not certain I suspect that here also carcinomatous areas in the tumor were overlooked. This patient had had a large ovarian cyst removed six years before we removed the second one and with it the uterus.

It is evident that the treatment of adnexal cancer is not very satisfactory. We may compare the results with those achieved in the treatment of cancer of other parts of the genital tract. In cancer of the cervix treated by operation Graves reported: an operability of 64 per cent; relative five-year cures of from 27.6 per cent to 34.2 per cent and absolute cures of 16.8 per cent to 18.5 per cent. Operation for cancer of the cervix has been displaced by irradiation for the results are just as good or better and the immediate risk is less. Thus Healy reports five-year cures in from 42 to 50 per cent of the cases, the result depending mostly upon the type of cancer cell and the stage of the disease. Ward reports five-year cures in 23.1 per cent of all cases and in 53.1 per cent of operable cases. Clark and Keene in their high amputation of the cervix with the cautery knife with the subsequent and immediate use of radium, report 42.9 per cent of five-year cures. So far as cancer of the fundus is concerned, Smith and Grinnell state that operative treatment in Graves's clinic achieved a relative curability for five years of 61.1 per cent in the early cases and 45.5 per cent in the later ones. Healy has recently reported a curability of 65 per cent in early cases and of 34 per cent in all cases, whether for three or for five years I was unable to determine. Taussig a year ago reported remarkable results in the treatment of cancer of the vulva; of 11 cases 9 remained free of recurrence for a period longer than five years, 81 per cent. Two of the latter women developed a recurrence later and died. This still leaves him a curability of 63.6 per cent.

THE IMPORTANCE OF AN EARLY DIAGNOSIS

As the early diagnosis of cancer is so important for successful treatment and as it seems to present unusual difficulties in cancer of the adnexa, I have undertaken in this paper to inquire: (1) What the early manifestations of adnexal cancer are; (2) why they are so often overlooked; and (3) whether anything more can be done to increase the proportion of cases that fall into the surgeon's hands at an early stage.

The basis for my remarks in addition to the literature upon the subject is an analysis of 28 malignant tumors of the ovary and 1 primary cancer of the tube occurring in 115 consecutive cases of ovarian tumor in the gynecologic service at the Jefferson Hospital from September, 1921, to January, 1930. In this work I have been ably helped by my assistant, Dr. John B. Montgomery.

SYMPTOMS

Age.—We may note at the beginning that adnexal cancer is a disease of late reproductive, menopausal or postmenopausal life.

In Wechsler's series of 192 cases of *tubal* cancer, 53 are stated to have passed the menopause; 66 per cent of the cases occurring between the ages of 40 and 55.

In Byron and Berkoff's series of cancer of the *ovary*, 48 per cent had passed the menopause, but a large proportion (31 per cent) had occurred before the age of 40.

Pain.—As the organs affected are internal there may be no well-marked symptoms such as the bloody discharge so commonly observed in other forms of genital cancer; no disturbance of function as is quickly manifested in cancer of the gastrointestinal and the urinary tract; no "lump" or "sore" to attract the patient's attention as in cancer of the skin or of the breast. Pain is the most common early symptom of adnexal cancer but very often it is not at all distinctive, being mild in degree and varying much in its location and character so that it is attributed not unseldom to innocent causes and regarded with indifference by the patient.

Bleeding.—Pain draws more interest in primary cancer of the tube than in cancer of the ovary because it is associated with a bloody discharge in a large proportion of the cases. In cancer of the ovary, bloody discharge is not a frequent symptom except after the menopause, when it also takes place in a considerable number.

Most writers mention pain as a symptom but dwell more particularly upon an increase in the size of the abdomen, the presence of a mass especially bilateral, loss of weight and ascites. Bleeding is prominently mentioned but almost any menstrual disturbance including delayed, scanty or absent periods have been reported.

The latter have been regarded as evidence of congenital deficiencies in the ovary or of destruction of the ovarian follicles.

In recent years more stress has been laid on pain and bleeding. Strauss says "the onset of ovarian cancer is insidious, usually with pain in the lower abdomen or back or both." Byron and Berkoff mention pain in the abdomen as the most frequent symptom occurring in 51.1 per cent of their cases, but they have noted also in addition that 19 per cent complained of backache, 12.7 per cent of bearing-down sensations, 9.5 per cent of dysuria and 3.1 per cent of painful defecation.

The significance of postclimacteric bleeding as an indication of ovarian newgrowths has been dwelt upon of late by a number of writers, notably Robert Meyer, Schiffman, Neuman, Novak and TeLinde. The recurrence of bleeding from the uterus is supposed to result from a renewal of the ovarian function. This stimulation to renewed activity has been ascribed especially to the so-called granulosa cell carcinomata and is evidenced by hypertrophy of the uterine body and a thickening of the uterine mucosa.

Robert Meyer reports seven cases. All of the patients were past the menopause. No definite statement is made of bleeding, but one may presume that it existed. The striking fact in all was the enlargement of the uterus (one of them contained a myoma) accompanying these ovarian tumors in postclimacteric life.

In our series pain was present in 78 per cent; but it was not the outstanding complaint; i.e., the symptom that brought the patient to us, except in a few. Nevertheless a review of the histories showed that in a majority of the cases pain had been the first symptom. But it was very often slight and very often connected with the function of the intestines or the bladder and so escaped the serious attention of the patient.

In 41 per cent of the postclimacteric cases in our series uterine bleeding was a prominent symptom and usually the one that actuated the patient to seek medical advice.

Before the menopause pain and bloody leucorrhea are easily referred to diseases of the reproductive period. During the menopause their significance to the patient may be obscured by the idea that as she is "changing" almost any pelvic disturbance may be expected. After the menopause the symptoms are much more striking especially if the bleeding and the pain are in combination.

Both Wechsler, and Wharton and Krock speak of pain as an early and constant symptom in cancer of the tube. Wechsler in his review of the literature finds that it occurs in the hypogastric, iliac, or lumbar regions, on the same side as the disease, and that it has been described as pulling, pressing, sticking, boring, lancinating, or cramp-like (the latter is most prominent); the pain is often paroxysmal and usually associated with sudden, profuse discharge from the vagina. He says that cancer of the tubes causes a danger signal much sooner than any other intraperitoneal malignant disease and that when a bloody discharge persists in patients within the cancer age, after a diagnostic curettage with negative findings, it is of extreme significance and attention should be directed toward the adnexa.

He speaks of a discharge as present in the vast majority of cases but the fluid assumes different hues, due to the frequent admixture of blood in various stages of decomposition. It has been described as amber, tea, meat-water, brownish, rose, or definitely bloody; the typical syndrome of hydrops tubae profluens appears in from 10 to 25 per cent of cases.

The most striking menstrual symptom is metrorrhagia in women after the menopause. In Wechsler's collection of 196 cases there were 53 that were postclimacteric. Leucorrhea was a prominent symptom in 9 and metrorrhagia in 30. In Wharton and Krock's series of 14 cases, 5 had passed the menopause and 4 had hemorrhage. Both of the author's patients were past the menopause and had a periodic bloody discharge.

It is not uncommon for primary carcinoma of the tube to advance beyond a curable stage during the course of observation or treatment. In the first one of the author's cases the patient complained of pain and bloody leucorrhea fully eight months before unmistakable evidences of adnexal cancer had made their appearance.

That such misfortunes have taken place before is evident from reports in the literature.

Bültemann reports a fifty-year-old woman in whom the operation was done 16 months after she came under observation. A diagnostic D and C had been performed immediately and then x-ray treatment in full castration dose on three occasions. Heil operated in November of 1924 on a woman of 46 in whom a simple

ovarian tumor had been known to exist since 1912. Severe hemorrhage and watery discharge started in January of 1924. Scott and Oliver report a case of watery and bloody discharge 12 years after the menopause. Curettage was negative. Symptoms continued and 11 years later operation showed carcinoma of the tube. Cameron reports a case in which a hysterectomy was done simply because a diagnostic curettage was impossible on account of a very narrow vagina. Barrows reports a case in which a posterior colpotomy within 4 months of the onset of symptoms was negative. An adnexal mass appeared on the left side within the succeeding 4 months. LeBalle and Patay in the report of an advanced case admit that they had not understood the significance of transuterine discharge of water and blood.

Ovarian cancer also is easy to overlook. The danger of doing so even in the presence of postclimacteric hemorrhage is well illustrated in three cases reported by Schiffman. We may mention the first as an example; the uterus was removed by vaginal hysterectomy on account of bleeding. It showed no evidence of malignancy and nothing abnormal was observed in the adnexa. Two years later the patient died with an advanced malignant tumor springing from the left side.

In another patient 70 years old, several days' bleeding had occurred eighteen years after the menopause. This was repeated eleven months later and four weeks before her admission to the hospital. Curettage showed hypertrophy of the uterine mucosa but no malignancy. Laparotomy revealed a carcinoma of the right ovary. In a third case, aged fifty-three, and three years past the menopause, there had been slight irregular bleeding. Curettage elsewhere had been negative. A few weeks later Schiffman did an exploratory section and found an ovarian carcinoma. The patient died and an autopsy revealed metastases to the brain.

One must not forget also that cancer of the ovary may be metastatic (as in 20.75 of Mayer's series) from the stomach, intestines, breast, etc., and that the history of previous or existing cancer in those parts may point the way to an earlier recognition of cancer of the ovary.

In our series of malignant ovarian tumors, an abdominal enlargement had been noted in 17 and was the principal complaint. The duration of symptoms—but this applies mostly to pain—had varied: in three it was only two weeks; in six less than six weeks; in six not more than twelve weeks; in seven the symptoms had gone on for a long time, i.e., seven months to two years, in six it was indefinite but probably of some length. An individual analysis of the cases showed some other interesting and instructive facts as follows:

In two cases a twisted pedicle with acute pain revealed sarcoma of the ovary at an early date. Both of these patients are alive, one seven, one eight years from the time of operation.

Two of the patients were aware of an abdominal tumor for years before surgical treatment was accepted. In the first operation had been repeatedly refused; in the second an abdominal tumor had been diagnosed as myoma and treated with the x-ray.

In one case the patient had had intrauterine irradiation for uterine cancer two years previously, hysterectomy at that time having been refused.

In one case intrauterine applications of radium to control bleeding the first time four years and the second time one year preceding admission had been made twice; no malignancy had been found in the uterus.

Two patients had undergone a radical operation for cancer of the breast fourteen years before the recognition of the ovarian tumor.

One patient had had an entire breast removed twenty-three years before but a positive diagnosis had not been recorded.

Three patients had had an ovarian cyst removed at a previous operation; the first fifteen years before with no record of the diagnosis available; the second four years previously, malignancy having been discovered, the third five months before, the malignancy not having been recognized.

Two patients not listed in this series as malignant died later of peritoneal carcinomatosis; no malignant areas had been found in the laboratory study of their specimens. One of the patients died within nine months, the terminal condition being verified by exploratory section; the other began to complain two and a half years after the operation. No exploratory section or autopsy was performed but the x-ray evidence of cancer of the lungs as well as of the abdomen was unmistakable.

INSTRUCTION OF WOMEN

The first part of an effort to increase the ratio of adnexal cancers that come to the physician at an early stage is such instruction of the laywoman as is needed to make her realize the possible significance of certain symptoms. It is hardly necessary to say anything more relative to the possible meaning of menstrual disturbances, leucorrhea and bloody discharge, although we should continue to remind her of it. But she ought to be advised that as the menopause is approached and for a while after, a periodic examination of the pelvis is desirable irrespective of symptoms and she should be informed that independent of abnormal bleeding or discharge from the vagina, lower abdominal pain of any degree, location or type—intestinal colic, dysuria or dyschesia, deserves thorough investigation. While such information will fill many women with unwarranted mental anxiety, they can be reassured completely, the purpose will be served and medical oversight can be provided.

The success of the endeavor to recognize cancer early is well known. There is no statistical evidence that the death rate has been lowered and it is questionable whether any can be expected. In medical centers it will be higher because more cancer patients go to them for diagnosis and treatment and therefore more are uncovered and treated and a greater number die there. Wainwright, of Scranton, has given definite statistical evidence that certain cancer cases apply to the physician earlier and are referred by him to the surgeon more promptly. He compared conditions at present with those of ten years before. Salzstein of Detroit, reported that at the end of a two weeks' period of intensive lay and medical education some 200 cases of cancer that had not been seen previously by any physician came under treatment. The same thing happened a year later. Fischel in St. Louis had much the same

experience. These facts have been supplied by Howard C. Taylor, President of the American Society for the Control of Cancer, who added, "If you had control, for example, of 100 women who were intelligent and would do as you told them and you were to correct all conditions in them that predisposed to cancer and then instructed them properly relative to the significance of symptoms that might appear and you cautioned them to report any of these conditions at once, is there any doubt that a definite number of these cases would be saved from dying of cancer?"

EDUCATION OF THE PHYSICIAN

What about the physician himself? Is he appreciative of what the early symptoms of adnexal cancer may be? Has he been sufficiently impressed with the fact that pain in the lower abdomen, not constant, not severe, often attributed by the patient to intestinal indigestion or bladder trouble or constipation calls for a searching examination of the pelvis? Has too much stress been laid in our teaching on abdominal enlargement, and a palpable mass in the pelvis as indicative of adnexal cancer?

I recall a physician's niece—she lived next door to him; for more than a year he had been giving her tablets for "intestinal indigestion"; there were no other symptoms; menstruation was normal. Finally the patient observed abdominal enlargement. Then for the first time an examination was made; the pelvis and abdomen were diffusely involved; ascites was present and nothing availed.

The physician should not only act at once when he is told of lower abdominal or pelvic pain but also in his contact with patients inquire for it, and advise without alarming, periodic interrogation and pelvic examination of all women at the cancer age.

PALPATION OF THE ADNEXA

When once the suspicion is aroused our chief diagnostic method is palpation of the adnexa. Unfortunately the parts are not accessible to direct inspection, curettage or biopsy, the patients are often difficult subjects for palpation of the ovaries and tubes; women at the time of life when the incidence of adnexal cancer is greatest usually have a fat abdomen, a thick omentum, good sized epiploic appendages and some contraction and loss of pliability of the vaginal vault. In quite a number of them without doubt it is impossible to say with certainty whether or not there is anything abnormal within the pelvis.

DANGER OF RADIUM

When the chief symptom is bleeding unless there is a ready explanation below the uterine cavity, diagnostic curettage is usually advised. If nothing malignant is found in the uterus and no enlargement of the adnexa can be made out, it is quite customary to apply

radium. In chronic metritis with and without benign hyperplasia of the endometrium and high blood pressure, this is a satisfactory plan. But the use of radium is attended with risk especially in patients beyond the menopause, if we forget the necessity of a careful study and observation of the patient beforehand, otherwise disorders of the adnexa will sometimes be overlooked.

Bleeding after the menopause with a small uterus and an atrophic endometrium is found in tubal cancer particularly. Bleeding after the menopause with enlargement of the uterus and hypertrophied endometrium especially suggests ovarian newgrowths. If radium is applied in either case on the strength of a negative curettage alone we may mask a continuance of a malignant adnexal disease.

Our attitude toward the use of radium as supplementary to curettage, whether it has shown endometrial hypertrophy or not, must be a conservative one. When we are in doubt as to the existence of adnexal disease, it will be better to defer the radium and trust to curettage alone for the relief of symptoms; meanwhile repeatedly observing and studying the patient.

POSSIBILITIES

There is a brighter side to the prospect for the adnexal cancer patient if the tumors are discovered early. This is the mark at which we aim. For example, Stübler and Brandess figured that of their unilateral and operable malignant tumors there was a curability of 55.3 per cent and Norris reported that in his series nearly 60 per cent of the cases that had appeared favorable at the time of operation survived for three years. In addition to operative removal as complete as is compatible with the condition of the pelvic organs and the general state of the patients, we have the help of postoperative x-ray treatment. Keene, Pancoast and Pendergrass show the results of such treatment in a report of 24 cases following exploratory section or operation for carcinoma.

In six an exploratory section only was possible, five of these had died at the time of the report and the sixth was dying. In 18 a partial or complete excision had been performed. Eleven died from two and one-half months to four years later, 7 were alive at the time of the report for varying periods of from seven months to four and one-half years. The authors conclude that irradiation often helps, but that it is impossible to predict its effect in a given case.

CONCLUSIONS

1. The prognosis of adnexal cancer is bad unless the disease is discovered at an early date.

2. The early symptoms of cancer of the adnexa are easy to overlook and in some instances definite enlargement of the adnexa cannot be demonstrated.

3. The prospects of cure improve directly in proportion to the stage of the disease although certain types of cancer are less favorable than others.

4. For the purpose of detecting the disease early the laywoman should be encouraged to report lower abdominal distress or discomfort of any sort as well as irregular bleeding or leucorrhea.

5. In under-graduate and post-graduate instruction more emphasis should be placed on the early symptoms of cancer of the adnexa and less on the late ones.

6. Periodic pelvic examination of women at the cancer age should be made, the examiner not focusing his attention too exclusively on the uterus and the external parts.

7. Repeated pelvic examination and continuous observation and study of the patient should be made in suspected cases if nothing is found at the first visit.

8. Examination under anesthesia may be advised in doubtful cases.

9. True ovarian tumors or any intrapelvic tumor of doubtful character should be removed without delay when the general condition of the patient is favorable.

10. Women who have had carcinoma elsewhere especially should be questioned and examined at regular intervals.

11. All ovarian tumors removed at operation require a painstaking laboratory study, and thorough postoperative irradiation should be employed in all positive and suspected cases.

12. Complete intraabdominal palpation and exploration is to be recommended when practicable during the course of operation for an ovarian tumor even though it appears to be benign.

13. When postclimacteric bleeding and discharge continue from the uterine cavity in spite of negative curettage for evidences of uterine malignancy, especially if there is pelvic pain or the bloody discharge is periodic, one may suspect an adnexal cancer; palpable enlargement of one or both sides under such circumstances warrants an exploratory incision.

14. When after careful study adnexal cancer is strongly suspected and yet no definite evidence of adnexal enlargement can be found upon palpation, exploratory section must come up for consideration. The ease of examination in the individual case has an important bearing on the decision. If the patient is thin and palpation of the affected parts is easy, the chance of overlooking an early cancer is small and one may rest content with watchful waiting. When the woman is fat and the examiner cannot be certain that he palpates definitely the ovary or the tube but suspects adnexal enlargement, exploratory section ought to be advised but only after the most complete study, con-

sultation with another gynecologist and a reliable internist, and a full explanation of the situation to the family and sometimes to the patient.

15. Caution should be observed in the use of radium for the purpose of stopping hemorrhage from the uterus when the reason for the symptom is not clear. This will apply especially to the postclimacteric period when the uterus and mucosa are hypertrophied and we suspect a cancer of the ovary or when the uterus and the endometrium are atrophic and we suspect a cancer of the tube.

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THE TREATMENT OF SALPINGITIS BY LOCAL INJECTION OF TURPENTINE

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THE high incidence of salpingitis among the patients admitted to the wards of any general hospital justifies the discussion of anything new in the manner of treatment. In the Scandinavian clinics, according to recent articles, the percentage of salpingitis runs almost to 40 per cent. In my own service in Montreal, from 1920 to 1924, 15 per cent of 2,100 cases were admitted for salpingitis. In the following five years only 11 per cent of 2,800 cases were admitted with the same diagnosis. To my mind the reason for this is that the cases were earlier recognized, thanks to the broad-minded action of the Quebec Government in establishing their venereal clinics and also to the fact that a change in treatment of the acute cases, particularly the use of nonspecific protein therapy and the discard of the tampon, have materially decreased the number of acute infections going on to salpingitis. During the same two periods of five years, I find an increase in the expectant treatment from 38 per cent to 50 per cent and a decrease in radical operations from 31 per cent to 18 per cent. It is noteworthy that these two series, 68 per cent and 69 per cent, respectively, leave approximately 30 per cent of cases which were treated by operation other than hysterectomy.

It is to be remembered that up to the time of Lawson-Tait in 1870, absolute conservative therapy carried with it a mortality of about 50 per cent. It is possible that only the worst cases were recognized, as the gonococcus had not as yet been identified and there is no doubt that for a time radical operation improved these results. About 1900 the desirability of operation in the acute cases was questioned and in 1909 Simpson[2] read before this Society his epoch-making paper on the value of delay in operation yet even today ultraradical treatment, removal of the uterus and both tubes, seems to be the preferred method of dealing with those cases not yielding to expectant measures.

At the British Congress in Manchester in 1927, it was noteworthy that most of the English and Scotch gynecologists favored operative therapy, from early operation to operation when safe, and even the most optimistic believers in expectant treatment admitted the necessity for radical operation in a fairly large percentage of cases.

Blair Bell[3] suggests that the conservation of the genital functions of the female, even though conception be impossible, is a surgical ideal, but claims that in only a small percentage of cases can the ovary be retained.

My reason for bringing before you this series of cases is to prove that in the vast majority of cases the ovaries may be safely conserved even when operation is undertaken in the acute stage. Operation, other than in the acute stage, is usually highly irrational. One side alone was frequently removed despite the knowledge that infection would in all probability recur on the opposite side, and to this has been added the evidence of Sampson as to the further danger of endometriosis where salpingectomy is done. It is well known that salpingectomy alone carries with it grave danger of involvement of the ovarian blood supply on the affected side.

One difficulty in dealing with this question is that though we speak of salpingitis as if it were easy to diagnose, such is not the case, at least such is not the case in Montreal, for my surgical colleagues admit a 20 per cent to 25 per cent error in diagnosis of female patients admitted for appendicitis. It is easy to say that acute salpingitis should not be operated upon, but consider the problem of the surgeon who opens the abdomen of some young woman and instead of an acute appendix finds an acute fallopian tube. A great deal of self-control is necessary to avoid doing something, and the results of some of the British gynecologists in dealing with salpingitis in the acute stage might be held to justify the removal of one or both tubes. Any attempts to dissuade from immediate operation, on the basis of the report of Aldridge[4] which appeared recently, dealing with the imperfect healing of wounds, excessive morbidity and mortality, shock and sepsis, are not, I believe, borne out by the results of Cameron and others who advocate operation in the acute stage. The most important problem in connection with salpingitis is the conservation suggested by Blair Bell which, however, is not achieved by the Bell-Beuttner operation.

I have already mentioned the use of nonspecific protein therapy in cases of acute salpingitis. This treatment was the result of observations of Klingmuller[5] of Kiel in 1918. While not specially dealing with gonococcus infection in females, Klingmuller noted marked improvement in certain patients with gonorrhea while undergoing treatment for other conditions, by means of intramuscular injection of small quantities of essential oil. This was undoubtedly due to general stimulation of the body tissues and was the basis of much further work, notably by Zoeppritz,[6] Sonnenfelt,[7] Kronenberg[8] and others who, while not claiming everything for the method of treatment, decided that it was at least harmless, and in many cases did good. About the same time Brewitt[9] reported twelve cases in which he had used similar inoculations directly at the site of the maximum evidence of infection, notably into the tubes. Brewitt's technic was to inject four or five cubic centimeters of a 10 per cent solution of turpentine in paraffin oil into the lumen of the tubes and also into their fused fimbriated ends after previous aspiration of pus. Any adhesions were released

and the omentum was brought down to Douglas' culdesac and fixed in such a manner as to separate the pelvis from the peritoneal cavity. All twelve cases recovered satisfactorily without much rise of temperature and their general condition was improved at once. On subsequent examination, four or five weeks later, the masses had disappeared, the uterus was mobile and the appendages were only slightly tender. Three of the twelve cases subsequently became pregnant.

Impressed with the success of the nonspecific protein therapy, in my own and other clinics, in the more acute gonorrheal infections, I started some ten years ago to try out the method suggested by Brewitt, but with a slightly different technic. The abdomen was opened in the midline, the peritoneum being protected by rubber sheeting, and the adhesions were then carefully released, either with the finger, or with blunt dissection. Tubal masses, when present, were evacuated by means of a syringe with a fairly large needle, after which the syringe was changed and the same needle used to inject a variable quantity of 10 per cent turpentine and oil. No attempt was made to prevent this solution from exuding into the pelvic cavity. The omentum was not brought down as Brewitt had suggested, but in each instance the uterus was suspended either by the Olshausen or the Baldy-Webster method. In some of the earlier cases catgut was used in making these suspensions, but I soon learned that the only satisfactory ligature for any suspensory operation was silk. Incidentally the appendix, involved in most of the cases, was removed in practically all.

In all, over two hundred such operations have been done, with only two deaths, but I wish to present certain features of the first seventy-five of these which have now stood the test for approximately five years.

I might say that at the British Congress of Gynecology and Obstetrics in 1927, Miss Ivens[10] reported a series of sixty cases treated with antigonococcal serum after opening the abscesses and mopping freely with normal saline. Her results compared more than favorably with other methods employed, but aroused little comment. The method I have been employing and that employed by Miss Ivens are very similar, but to use Miss Ivens' own statement, "antigonococcal serum to be efficacious must be used early, while the turpentine injections are as satisfactory in the chronic as in the acute cases." I would also mention that other fluids have been noticed as having favorable effect when injected: Nahmacher,[11] iodipin; Schmitz,[12] lipiodal; and Davis,[13] mercurochrome.

While the exact method of operation of these substances remains doubtful, in a number of our cases very profuse uterine discharge was noted three to four days subsequent to the injection and it would appear as if a stoppage of the lumen of the tube at the uterine end had

TABLE I

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
3370	Pain in abdomen; weakness.	Yes	Very dense adhesions; pyosalpinx. Hysterectomy would have been unsatisfactory.	Immediate—Improved. Afebrile. No pain. Later—Pelvis O.K.
5662–22	Pain in back and lower abdomen. Bleeding.	No	Tubes closed. Left ovary size of pigeon's egg. R. test negative November 23.	Immediate—Improved. Pelvic ex. negative. Later—11/4/25. Feels fine. No bleeding. Pelvis O.K.
4805–22	Pain in lower abdomen. Purulent discharge.	Yes	Right tube densely adherent. Left tube densely adherent to ovarian cyst.	Immediate—Improved. Masses right and left not tender. Clinically O.K. Later—1/9/24. Better than ever. No pelvic pain. Menses regular.
3382–22	Heavy dragging pain L.L.Q.	Prob.	Left hydrosalpinx. Right tube closed not distended.	Immediate—Improved. No mass. No tenderness. Later—1/9/24. Much better. No pain in pelvis. Menses regular.
5492–22	Dyspareunia. Leucorrhea.		Right hydrosalpinx. Left hydrosalpinx.	Immediate—Improved. No pain. Uterus mobile. Fullness on left. Right O.K. Later—1/12/23. No pain since. Slight thickening on left.
5753–22	Pain in left and right lower quadrant. Pain in right hip.	Yes	Tubes red and inflamed, left closed.	Immediate—Improved. Slight tenderness over tubes. No mass. Later—Nov., 1925. O.K.
2504–24	Pain in right lower quadrant.	Yes	Left tubo-ovarian mass. Right tube tortuous and fixed.	Immediate—Improved. No temperature. No pain. Later—Nov., 1925. Profuse leucorrhea. No pain. Fullness on left. No tenderness.
3406–23	Pain left lower quadrant. Leucorrhea.	Probable	Large tubo-ovarian mass.	Immediate—Improved. Tenderness both fornices. Later—Aug., 1923. No pain tubes. Sept., 1923. Free from pain. Soft mass in culdesac. Dec., 1923. No complaints. Oct., 1926. Negative pelvis.
2612–23	Pain lower abdomen; fever; nausea; menorrhagia.	Yes?	Tubes enlarged, boggy in culdesac.	Immediate—Satisfactory. Later—Oct., 1923. No better. TBC?

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
4099–23	Pain in lower abdomen. Leucorrhea.	?	Uterus retroverted. Left ovarian abscess. Left tube dilated. Right swollen and tortuous.	Immediate—Improved. Pelvic mass felt under anesthetic. Following examination temperature fell. Later—Sept., 1923. Improved. Right hydrosalpinx. Left clear.
4192–23	Pain right lower quadrant.		Both tubes occluded. Left fixed to ovary.	Immediate—Improved. Slight thickening both tubes. No tenderness. Later—July, 1924. No pain since. Small left sided mass not tender. Menses regular. Nov., 1925. No tenderness, pain or mass.
472–23		No	Right ovary cystic, tube occluded. Left tube partly patent.	Immediate—Improvement good. Later—Sept., 1924. Condition excellent.
1611–25	Pain in lower abdomen.	Probable	Old and recent adhesions. Tubo-ovarian mass left.	Immediate—Improved. T.O. masses smaller. Later—Nov., 1925. Slight tenderness on movement of uterus. No mass. Premenstrual pain only.
1182–25	Pain in lower abdomen. Leucorrhea.		Old adhesions both sides. Right tube occluded. Left tube glued at fimbriated end.	Immediate—Improvement good. Later—Nov., 1925. Much improved. No masses. Able to work. Slight tenderness over appendages.
3125–25	Pain in right lower quadrant.		Tubo-ovarian mass left. Pregnant uterus.	Immediate—Improvement good. Slight tenderness over left appendages. Later—No mass felt on left. No pain. Patient complains of slight pain on right but no mass is felt. Oct., 1926. Negative pelvis. Live baby full term.
McK–1925	Menorrhagia.	No	Dense adhesions due to tuberculosis.	Improved. Later—Nov., 1925. No pain. Much more comfortable.
2858–25	Vaginal bleeding. Pain in lower abdomen.	Prob.	Large tubo-ovarian mass right. Left chronic tube—adherent to ovary.	Improved. Slight tenderness on left. Lost.

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
509–24	Pain in back and R.L.Q. Leucorrhea.	No	Cystic ovaries, no adhesions. Tubes kinked. Uterus retroverted.	Improvement good. Later—Aug., 1924. O.K.
1076–25	Irregular bleeding. Leucorrhea.	No	Early ectopic right.	Improvement excellent. Later—Nov., 1925. Negative pelvis.
2542–25	Pain in lower abdomen.	Prob.	Appendages adherent in culdesac. Uterus retroverted.	Improvement excellent. Later—Nov., 1925. No pelvic pain. Uterus freely movable—no pain.
4470–25	Pain in left lower quadrant.	No?	Right tube thickened. Left occluded by adhesions.	Improved. Tenderness over appendages, but no pain. Lost.
1158–25	Discomfort in lower abdomen. Leucorrhea.	Possible	Left tube closed by adhesions. Right hydrosalpinx. Cystic ovary.	Improvement good. Later—Nov., 1925. No pain. Menses. Some thickening on left.
4059–24	Pain in abdomen. Vaginal bleeding.	Prob.	Right tube thick and tortuous. Left tube less thickened.	Improvement good. Later—Oct., 1925. Pain in back lately and discharge. Right tube is behind uterus, tender.
3428–24	Pain in lower abdomen. Metrorr. and menorrhagia. Leucorrhea.	Prob. not	Very few adhesions about tubes which were patent.	Improvement good. Later—No tenderness in pelvis.
3037–24	Pain in lower abdomen. Leucorrhea and constipation.	No	Little evidence of P.I.D. Left tube hydrosalpinx. Right ovary cystic.	Improvement good. Later—Jan., 1926. No tenderness. No dysmenorrhea. Tubes palpable, but not tender.
2888–25	Pain in lower abdomen. Metrorrhagia.	Yes	Unruptured ectopic right. Subacute salpingitis left.	Improvement fair, febrile, no tenderness. Later—Aug., 1925. Pelvis negative.
5746–22	Pain in right lower quadrant.	No	Both tubes very red. Right ovary cystic.	Much improved. Later—Jan., 1927. Condition O.K.
5265–22	Pain left costal margin. Abdominal pain.	?	Tubes red and patent. Uterus retroverted. Some adhesions.	Improved. No pain. Later—Aug., 1923. No pain since. Pelvis clear.
4637–22	Pain in lower abdomen. Bleeding.		Uterus retroverted. Left hydrosalpinx. Right pyosalpinx.	Improved. No pain on movement of uterus. No mass. Later—Dec., 1923. O.K.

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
4555–22	Pain in R.L.Q.	Prob.	Large right tubo-ovarian mass. Many adhesions on left.	Improved. No pain on movement of uterus. Right side O.K. Left tube palpable. Later—Nov., 1925. O.K. until last 6 mo. when she has had pain. Left tube enlarged (married at time of recurrence).
3555–22	Pain in R.L.Q. (D & C). Leucorrhea.		Tubes tortuous. Occluded filled with clear fluid.	Improved. No tenderness or fluid. Later—Jan., 1923. Excellent. No pelvic inflammation.
60–23	Pain in R.L.Q. Vomiting.	Prob.	Tubes injected.	Improvement good. Later—March, 1923. Uterus drawn to left, rather firmly fixed. Nov., 1925. Able to work. Occasional pain.
3663–23	Pain in R.L.Q. Dysmenorrhea.		Tubes congested but patent.	Pain not relieved. Later—Renal calculus removed.
1881	Premenstrual vomiting. Lower abdominal pain.		Double hydrosalpinx.	Improved. Excellent. No pain. Later—Nov., 1925. No pain or tenderness. Negative pelvis.
4270–23	Leucorrhea. Recurrent abd. pain.		Adhesions both sides. Tubo-ovarian mass on left.	Improved. Some tenderness high on left side. Later—Nov., 1925. Pelvis negative.
6313–23	Pain in lower abdomen. Leucorrhea.		Adhesions in culdesac. Tubes injected.	Improved. No pain.
4920–23	Pain in left lower quadrant.		Adhesions between tubes and ovaries.	Lost case. Improved. No tenderness. Slight thickening on left. Later—Oct., 1923. Well. Anatomically O.K.
4908–23	Pain in lower abdomen. Leucorrhea.	Yes	Adhesions both sides.	Improved. Left appendages palpable. Not tender. Lost—did not return to out patient department.
4505–23	Pain in lower abdomen. Yellow discharge.	Yes	Right pus. 10 c.c. pus in tube. Left tube occluded.	Improved. Appendages thickened but not tender. Later—Dec., 1923. Feels better. Still has profuse leucorrhea.

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
4773–22	Pain in lower abdomen.	No	Left tube tortuous and swollen. Right tube tortuous and more distended.	Improved. Mobile without pain. Slight tenderness in culdesac. Right free. Later—Tender left side. No pain.
1231–23	Pain in R.L.Q. Disturbance of menstruation.		Right hydrosalpinx. Left tube occluded.	Improved. Slight fullness of left appendages. Later—Nov., 1925. No pain. Menses regular. No tenderness or masses.
3994–23	Bleeding.		Right tube size of hen's egg. Left occluded.	Improved. No pain.
3516–23	Pain in lower abdomen.		Uterus retroverted. Abscess right ovary 2 oz. pus. Left tube large and edematous.	Improved. Febrile on discharge 1927. Patient well. O.K.
4559–23	Pain left lower quadrant. Leucorrhea.		Uterus retroverted. Right tube tortuous, patent. Left tubo-ovarian mass.	Improved. Appendages not tender. Thickening on left. Case lost—did not return to out patient department.
4280–23	Pain lower abdomen. Profuse leucorrhea.		Left hydrosalpinx. Right adhesions.	Improved. Tender mass on right. Smaller mass on left. Later—Sept., 1923. No pain.
4347–23	Pain in lower abdomen. Leucorrhea.		Tubes fairly normal. Right occluded. Ovaries cystic.	Improved. Some tenderness left fornix. Some white discharge. Later—Did not return to out patient department.
4329–23	Irregular menses. Profuse leucorrhea. Pain in lower abdomen.	Yes	Very dense adhesions. Right pyosalpinx. Tubes tortuous.	Improved. Tenderness gone. Later—Oct., 1923. No pain. Better than ever. Miscarriage 1 year after. Oct., 1926. Negative pelvis.
M–23	Pelvic pain.	?	Adhesions involving both tubes and suggesting chronic salpingitis.	Nov. 6, 1925. Tubes palpable. No pain. Endocervicitis some days. Pregnancy with abortion, 1926.
5241–25	Pain in lower abdomen. Leucorrhea.		Bilateral hydrosalpinx. Right salpingo-oöphorectomy.	Nov., 1925. No pain. Left appendages slightly tender.
2687–24	Pain in epigastrium and left lower quadrant. Gas.		Bilateral hydrosalpinx.	Nov., 1926. No pain since. Negative pelvis.
915–26	Pain in lower abdomen. Bleeding.		Left tube distended. Right edematous. Pregnant uterus?	Immediate—Uterus mobile. Left appendages palpable. Right O.K.

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
1971–26	Pain in lower abdomen.		Tubo-ovarian mass right. Left tube adherent.	Immediate—Patient died of peritonitis.
267–26	Pain in lower abdomen. Menorrhagia.		Tubo-ovarian mass left, size of golf ball. Right injected.	Immediate—Negative pelvis.
3095–26	Abdominal pain.		Tubes inflamed.	Immediate—Uterus mobile without pain. Later—Jan., 1927. Pelvis negative. Feeling fine.
4066–26	Pain in R.L.Q.		Adhesions both sides. Right hydrosalpinx.	Immediate—O.K. Later—Dec., 1926. Negative pelvis.
2805–22	Pain in lower abdomen.		Bilateral tubo-ovarian masses.	Immediate—Uterus mobile without pain. Appendages not felt.
4280–26	Pain in lower abdomen.		Uterus retroverted. Tubes relatively free.	Immediate—No tenderness in pelvis. Later—Jan., 1927. Negative pelvis except for palpable right appendages.
62–26	Pain in lower abdomen. Leucorrhea.		Uterus retroverted. Pyosalpinx both sides.	Immediate—Uterus mobile. No pain. Later—Patient did not return.
1676–26	Leucorrhea.	Yes	Right tubo-ovarian mass 5 cm. thick. Left tube 75 c.c. pus withdrawn.	Immediate—Uterus forward fixed. Large mass on right. Not tender. Later—Thickening both appendages. No tenderness.
4844–26	Pain in left lower quadrant. Metrorrhagia.		Dense adhesions.	Immediate—O.K. Later—Uterus mobile. No pain. Dec., 1926. Jan., 1927 uterus back causing pain.
5024–26	Weakness; discharge. Difficult urination.	Yes	Large pyosalpinx both sides.	Immediate—Uterus fixed in front with large mass. No tenderness. Later—Dec., 1925. Right side clear. Left non-tender mass.
4174–26	Pain in lower abdomen.		Tubo-ovarian mass right (out).	Immediate—Right side free. Left tubo-ovarian mass not tender. Later—Jan., 1927. O.K.
2593–26	Pain in right lower quadrant.		Tubes seem O.K. Large ovaries.	Immediate—O.K. Later—O.K.
5414–26	Sore abdomen.		Bilateral masses.	Immediate—Uterus mobile with some pain. Mass on right not tender.

TABLE I—CONT'D

HOSP. NO.	COMPLAINT	GONOCOCCUS	CONDITION FOUND	RESULT
5495–26	Bleeding from vagina.	No	Tubo-ovarian mass left.	Immediate—Uterus forward mobile. Left appendage large and tender. No pain if not touched. Later—Dec., 1926. Mass on left. Not tender.
5478–26	Bearing down pain.		Bilateral hydrosalpinx. Removal left side. Right turpentine suspension.	Immediate—Uterus mobile without pain. Right app. palpable not tender. Left O.K. Later—April, 1926. Old complaint. Uterus in good position. Right side negative. Left tender.
5327–26	Pain in lower abdomen.	Yes	Tubes distended. Turpentine to both.	Immediate—Smooth. Later—Dec., 1926. Large cyst mass on left not tender. Uterus mobile. Right side free.
1756–25	Pain in left lower quadrant.		Ovarian abscess left. Operation hysterectomy. Left salpingo-oöphorectomy. Right turpentine.	Immediate—No tenderness in pelvis.
1741–26	Pain in lower abdomen.		Right salpingectomy. Left turpentine. Fixation of uterus.	Immediate—Satisfactory. Later—Left tube palpable not tender. Uterus was fixed, gives some pain with periods.
1127–26	Abdominal pain.	Yes	Left salpingo-oöphorectomy. Right turpentine.	Immediate—Uterus in good position. Appendages clear. Later—May, 1926. O.K.
915–26	Bleeding.		Both tubes distended. 2 c.c. turpentine.	Immediate—Improved.
409–26	Pain in left breast.		Tubo-ovarian mass left. Right tube fused.	Immediate—Improved. Later—Jan., 1927. O.K.
1390–26	Pain in R.L.Q.		Left tube adherent to cystic ovaries. Right occluded.	Immediate—Satisfactory. Later—Satisfactory.
2281–26	Metrorrhagia.		Tubes thick 10-20 c.c. turpentine.	Immediate—Satisfactory. Later—Pelvis O.K.
2165–26	Menorrhagia. Ectopic history.		Intraligament cyst left ovary. Dense adhesions right.	Immediate—Satisfactory. Later—Satisfactory.
605–26	Leucorrhea.		Right ovarian abscess. Tube fused. Left tube open.	Immediate—O.K. Later—June, 1926. Negative pelvis.

been overcome. Certainly the fluid does not remain as such, as I was fortunate in securing, at a subsequent operation for another condition, the tube of a patient who had been "turpentined," which in this instance contained a limpid fluid negative to tests for oil and for turpentine.

A brief résumé of each of seventy-six cases is appended. The odd case was added on account of the clinical interest, though not a case of salpingitis. This, a woman who previously had been operated upon for extrauterine pregnancy, was admitted with a mass in the left side and some evidence of mild peritonitis. The diagnosis lay between tubo-ovarian mass and extrauterine pregnancy, but at operation it proved to be an ovarian abscess, together with an intrauterine pregnancy. The large ovarian abscess was evacuated by means of a needle, the pus replaced by the turpentine solution and the patient went to term and was delivered of a normal live child and a subsequent examination showed no evidence of the previous pathologic condition.

The predominating symptoms complained of by these patients were: pain, 61; leucorrhea, 22; bleeding, 19; dysmenorrhea, 2; vomiting, 2.

On examination definitely palpable pelvic masses were noted in fifty-three cases. In only four instances was the presence of a mass not associated with pain. Of the sixty-one patients (80 per cent), complaining of pain on admission, 56 were absolutely free from pain at discharge and have remained so since. Three were definitely improved, two of these noting pain only at the menstr. period. One, a tuberculous case, was no better, and one patient [illegible]. It is noteworthy that the pain recurred in those cases where th. suspension was not a success. Of fifty-three patients with pelvic masses, thirty-five at subsequent examination had no palpable mass in the pelvis. Thirteen others examined within six months were definitely improved, though the appendages were still definitely enlarged. Of these thirteen, six returned for but one examination, and four others failed to return for even one subsequent examination. The irregular and profuse bleeding was benefited immediately in practically all the cases, though three of the twenty-two were subsequently admitted for recurrence of bleeding, though this was unaccompanied by pain. We have tried in these cases the suggestion of Polak,[14] deep x-ray therapy, and believe that this will give success.

One death occurred in a patient with a large ovarian abscess which had been diagnosed as salpingitis. Here, the body of the uterus and the affected side were removed and the relatively free tube was turpentined and retained. This patient died of peritonitis. In the light of present experience I am of the opinion that aspiration of this abscess and the use of turpentine might have been satisfactory, but at that time I was not aware that large quantities, even up to 70 cubic centimeters, could be used without danger of untoward symptoms.

Though not primarily undertaken in the hope that these patients would become pregnant, four did so, though of these three aborted and the fourth was interrupted just before term on account of toxemia of pregnancy. This seems in line with the reports of Ritter[15] of Tübingen, who has given the result of sixty-five cases of salpingostomy with only four subsequent pregnancies, of which one went to term. It would appear that the apparent severity of the infection has little bearing upon the possibility of pregnancy, as may be noted from the following case:

Series 47, R. Came in, in October, 1922, complaining of menorrhagia and metrorrhagia, pain in the lower abdomen and pain on micturition and defecation. Since the birth of her only child one year previously, the periods have been irregular and for the past two months she has menstruated twice, each time for a period of ten days and has had between times a profuse yellow discharge. The pain is severe and cramp like, irradiating down to the thighs and has been fairly constant. Urination is frequent and painful, the bowels constipated and great pain associated with defecation.

On vaginal examination there was noted a profuse bloody discharge, the uterus forward and fixed, on the left a large tender fluctuating mass and on the right definitely enlarged and tender appendages.

At operation there were extremely dense adhesions involving both the large and the small bowel. Release of the adhesions resulted in damage to the peritoneal coats of the bowel and allowed the escape of free pus.

The tubes were occluded, tortuous, thick and filled with pus and both ovaries were n- disorganized. The adhesions here were freed as far as possible, the ovaries up behind the uterus, the pus evacuated by means of a large needle and the s filled with 10 per cent turpentine and oil. Owing to the extent of the raw area sulting from the freeing of the adhesions, a gauze wick was passed through the culdesac into the vagina. This patient became pregnant twelve months after operation and aborted in February, 1924, a fetus of approximately three months.

Since the adoption of this method of treatment practically all of the general surgeons in the Montreal General Hospital have made use of it and are continuing to do so. Apart from the death above noted and one other associated with generalized tuberculosis accompanied by gonorrhea, there have been no deaths among patients upon whom this treatment was used. In neither was it the cause of death. In the series above recorded there was but one case of infection in the abdominal wound, though more recently we have had trouble, particularly with cases which subsequently proved to be tubercular. It has been used not only in the chronic cases but in the very acute and as noted before up to 70 cubic centimeters of the solution has been injected without ill effect.

May I repeat that none of these women were spayed, that in 90 per cent of the cases they were permanently relieved of pain, that in the vast majority of instances inflammatory masses ultimately disappeared within a period of four to six months, sooner when medical diathermy

was used, that relief seemed to be permanent and in the scattered cases of recurrence it was obviously reinfection from without. The method is simple and absolutely safe and particularly adapted for use in general surgery.

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